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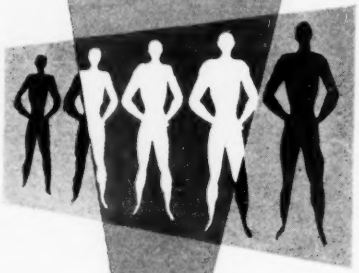

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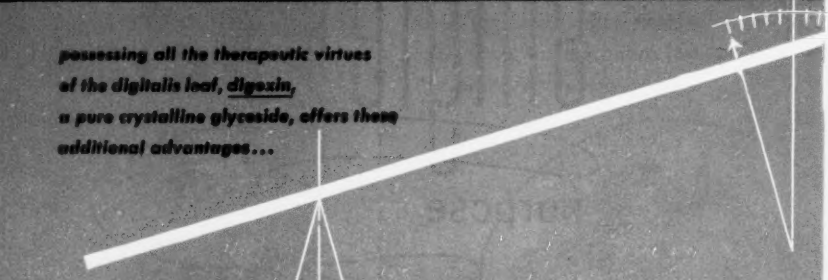

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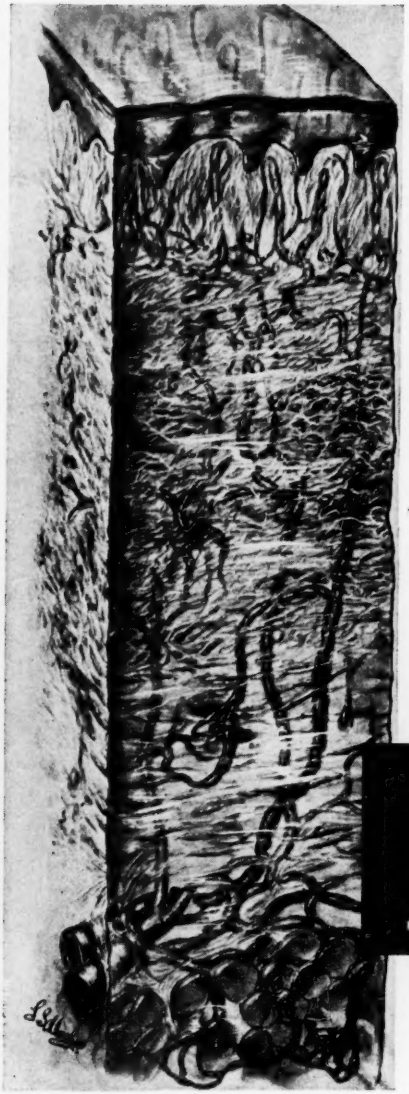

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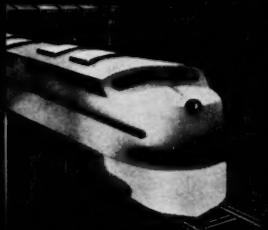

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SYMPTOMS ATTRIBUTABLE TO COLD HEMAGGLUTINATION

Report of Two Cases

JEANNE C. BATEMAN, M.D.*

WASHINGTON, D. C.

THE PHENOMENON of cold hemagglutination was recognized fifty years ago and gave rise to an extensive foreign literature during the first part of this century. Since its relationship to primary atypical pneumonia was pointed out by Peterson, Ham and Finland,[1] in 1943, the subject has received considerable attention in this country. Whereas cold hemagglutination was originally regarded as a phenomenon of mainly academic interest, it became increasingly evident not only that it was a valuable diagnostic aid in some epidemics of primary atypical pneumonia but that it could give rise to certain definite symptoms occasionally serious in character and directly related to intravascular hemagglutination. Agglutination of all types of red blood cells at cold temperatures by serum, with reversal at warm temperatures, occurs in a wide variety of conditions.[2] Cold hemagglutination appears to be transient in acute infectious diseases, in trypanosomiasis, in acute hemolytic anemia and in some cases of acquired chronic hemolytic anemia, but possibly permanent in cirrhosis of the liver, in Raynaud's syndrome (acrogangrene) and in some cases of acquired chronic hemolytic anemia.[2b]

The presence of cold hemagglutinins is suspect when there is difficulty in blood-counting procedures or cross matching of blood at room temperatures, or the development of acrocyanosis and hemoglobinuria are noted following exposure to cold. Gangrene of a part may develop if exposure is prolonged.[3] Less commonly, thrombotic phenomena are manifest.

* Formerly Instructor in Medicine, New York University College of Medicine, and Assistant Visiting Physician, Third Medical Division, Bellevue Hospital.

1. Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, Science **97**:167 (Feb. 12) 1943.

2. (*a*) Finland, M.; Peterson, O. L.; Allen, H. E.; Samper, B. A., and Barnes, M. W.: Cold Agglutinins: I. Occurrence of Cold Isohemagglutinins in Various Conditions, J. Clin. Investigation **24**:451-457 (July) 1945. (*b*) Stats, D., and Wasserman, L. R.: Cold Hemagglutination—an Interpretive Review, Medicine **22**:363-424 (Dec.) 1943.

3. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities, Arch. Int. Med. **72**:506-517 (Oct.) 1943.

One of the puzzling but important practical factors in the study of cold hemagglutination is its relationship to thrombotic phenomena and to intravascular hemolysis. Deposition of fibrin and actual thrombus formation probably occur only after prolonged vascular obstruction and stasis resulting from the intravascular agglutination which has been precipitated by the action of the cold hemagglutinins on exposure to cold. Stats [4] found that blood containing potent cold hemagglutinins was readily hemolyzed when shaken in the cold. Normal blood, with low titers of cold hemagglutinins, was not hemolyzed by shaking. Other authors [5] also found an apparent increase in mechanical fragility of red blood cells which were subject to cold hemagglutination. The process of agglutination usually seems to change the surface of the blood corpuscles in such a manner that they become more susceptible to the physiologic mechanisms of hemolysis.

Hemolysis in the presence of cold hemagglutinins is unaffected by complement and occurs in heat-inactivated serum, unlike the Donath-Landsteiner phenomenon, which requires complement.[4] Ernstene and Gardner [6] reported a positive reaction to the Donath-Landsteiner test in the case of a patient who had no history of syphilitic infection but in whom acrocyanosis and hemoglobinuria developed on exposure to cold. After sympathectomy the reaction to the test became negative, the cold hemagglutinin titer being unaltered. A positive reaction to the Donath-Landsteiner test is, however, usually unobtainable for patients with cold hemagglutination which is apparently unrelated to syphilitic infection. It has been suggested [7] that the same mechanism may be responsible for an elevation of cold hemagglutinin titer and for a seropositive reaction in the absence of syphilis.

The relationship of sulfonamide therapy to intravascular hemolysis in the case of a patient with potent cold hemagglutinins has been thought to be possibly more than casual; yet, it is apparent that the dramatic

4. Stats, D.: Cold Hemagglutination and Cold Hemolysis, J. Clin. Investigation **24**:33-42 (Jan.) 1945.

5. (*a*) Whittle, C. H.; Lyell, A., and Gorman, M.: Reynaud's Phenomena with Paroxysmal Hemoglobinuria Caused by Cold Hemagglutinins, Proc. Roy. Soc. Med. **40**:500-502 (July) 1947. (*b*) Finland, M.; Peterson, O. L.; Allen, H. E.; Samper, B. A., and Barnes, M. W.: Cold Agglutinins: II. Cold Isohemagglutinins in Primary Atypical Pneumonia of Unknown Etiology with a Note on the Occurrence of Hemolytic Anemia in These Cases, J. Clin. Investigation **24**:458-473 (July) 1945.

6. Ernstene, A. C., and Gardner, W. J.: The Effect of Splanchnic Nerve Resection and Sympathetic Ganglionectomy in a Case of Paroxysmal Hemoglobinuria, J. Clin. Investigation **14**:799-805 (Nov.) 1935.

7. Lubinski, H., and Goldbloom, A.: Acute Hemolytic Anemia Associated with Autoagglutination with a Thermal Amplitude of 0 to 37 C., Am. J. Dis. Child. **72**:325-335 (Sept.) 1946.

incidents of sudden massive hemolysis or thrombosis, now often attributed to sulfonamide therapy, took place before these drugs were used.

Data in cases in the literature presenting the symptoms of cold hemagglutinins have been compiled in table 1. These symptoms include acrocyanosis, thrombotic phenomena, hemoglobinuria and/or hemolytic anemia. They may occur separately but are frequently associated. Possible contributing factors are sulfonamide therapy and syphilis.

It will be noted that the majority of cases occur in the third, fourth and fifth decades, with the greatest incidence in the fourth. The greater incidence in males than in females may be partly due to more frequent exposure to cold, with consequent greater likelihood of development of symptoms. A great variance exists in reported titer. It should be remembered that neither the methods used for determination of cold hemagglutination titer nor those for collecting and storing of blood samples are uniform. Atypical pneumonia may be assumed to have been present in more than half these cases. Approximately 1 patient in 4 received sulfonamide therapy. A positive reaction to a blood test for syphilis appears to have been merely coincidental, though the possibility of a "false positive" reaction must be considered. In 42 cases, acrocyanosis occurred 13 times; thrombotic phenomena, 6; hemoglobinuria, 12, and various degrees of anemia, 21. Anemia in some cases was extremely sudden in onset and extremely severe in grade. Dramatic hemolytic crises have been reported in cases of primary atypical pneumonia in which the patients did not receive sulfonamide therapy,[8] in cases of primary atypical pneumonia in which the patients were treated with sulfonamide drugs[9] and spontaneously in the case of 1 apparently well person.[10] All these patients presented symptoms which were apparently directly attributable to the presence of cold hemagglutinins.

REPORT OF CASES

Case 1 is an example of vascular occlusion occurring in a case of primary atypical pneumonia accompanied with an elevated cold hemagglutinin titer.

Case 1.—N. O., a bartender of 22, was admitted on Nov. 21, 1945 to the Third Medical Division of Bellevue Hospital with complaints of a chilly feeling, fever,

8. Ginsberg, H. S.: Acute Hemolytic Anemia in Primary Atypical Pneumonia Associated with High Titer Cold Agglutinins, New England J. Med. **234**: 826-829 (June 20) 1946.

9. (*a*) Layne, J. A., and Schemm, F. R.: Acute Macrocytic Hemolytic Anemia Following Administration of Sulfadiazine, J. Lab. & Clin. Med. **29**:347-351 (April) 1944. (*b*) Platt, W. R., and Ward, C. S.: Cold Isohemagglutinins: Their Association with Hemolytic Anemia and Multiple Thrombosis in Primary Atypical Pneumonia, Am. J. Clin. Path. **15**:202-209 (May) 1945.

10. Currie, J. P.: Acute Hemolytic Anemia: Case Presenting Hitherto Unreported Features, Brit. M. J. **2**:8-10 (July 1) 1944.

TABLE 1.—*Cases Presenting the Symptoms of Cold Hemagglutination*

Source	Age	Sex	Race	Highest Cold Agglutinin Titer	Symptoms: Atypical Pneumonia	Sulfonamide Therapy	Acrocyanosis	Thrombotic Phenomena	Hemoglobinuria	Syphilis	Hemolytic Anemia
McCombs, R. P., and McElroy, J. S.: Arch. Int. Med. **59**: 109-117 (Jan.) 1937	57	M	W	1:1,024	—	—	Digits, nose, ears	*	+	—	Hemoglobin 10.5 to 11.5 Gm./100 cc.
Peterson, Ham and Finland [4]	(3 patients)			1:160 to 1:320	+	+					+ (degree not determined)
Lubinski and Goldbloom [7]	11	M	W	1:4 at room temperature	History suggestive	—	—	—	—	+	Hemoglobin 4.05 Gm./100 cc.; red blood cells, 1,390,000
Horstmann, D. M., and Tatlock, H.: J. A. M. A. **122**: 360-370 (June 5) 1943	47	F	W	1:1,024 Pronounced agglutination at room temp.	+	+		—	+	—	Hemoglobin 4.1 Gm./100 cc.; acute crisis
Layne and Schemm [9a]	36	F	W	.....	Bronchopneumonia	+	—	—	—	—	Hemoglobin 3.71 Gm./100 cc.; red blood cells 1,270,000; acute crisis
Finland, Peterson, Allen, Samper and Barnes [5b]	35	M	N	1:160	—	—	—	—	—	+	+
	45	M	N	1:2,560	—	—	—	—	+	+	+
	45	F	W	1:2,560	—	—	—	—	+	—	—
	34	M	N	1:80	—	+	—	—	—	—	+
Finland, Peterson, Allen, Samper and Barnes [5a]	(11 patients)			1:40 to 1:5,130	+	+	—	—	—	..	+
Stats and Bullowa [3]	69	M	N	1:3,200	—		Extremities	†	+	Kahn —; Wassermann —; Mazzini 2+	Hemoglobin 84 per cent
Platt and Ward [9b]	30	F	W	1:256	+	+	—	Multiple; severe	+	Kahn —	+; Hemoglobin 4.7 Gm./100 cc.; red blood cells 1,990,000
Benians, T. H. C., and Fensby, W. R.: Lancet **2**: 479-480 (Oct. 25) 1941	52	F	W	1:1,000	—	—	Feet, nose, ears, hands	—	—	—	Hemoglobin 50 per cent; red blood cells 3,000,000
	65	F	W	1:4,000	—	—	..	—	—	—	Hemoglobin 52 per cent
Helwig, F. C., and Freis, E. D.: J. A. M. A. **123**: 626-628 (Nov. 6) 1943	38	M	W	1:5,000	+	—	Nose, ears, hands	—	—	—	?
Bonnin, H.; Dubarry, J.; Dulong de Rosnay, C., and Lucas, P.: Sang **18**: 269-280, 1947	46	M	W	1:1,280	Questionable; virus infection	—	Extremities	—	—	Kahn —	Hemoglobin 80 per cent; red blood cells 3,630,000
Hanns, A.: Sang **15**: 506-525, 1942	45	M	W	1:1,000	—	—	Ears, nose	—	+	Wassermann —	Red blood cells, 2,800,00
Currie [10]	37	M	W	No titer; clumping at room temp.	—	—	—	—	+	Wassermann —	Hemoglobin 15 per cent; red blood cells 900,000
Le Goff, J. M.: Presse méd. **4**: 628-629 (April 19) 1933	36	M	..	No titer		—	+	+	—	..	
	78	F	..	No titer			+	..	—	..	
Forbes, G. B.: Brit. M. J. **1**: 598-600 (May 3) 1947	24	M	..	1:1,024			Fingers	—	—	Wassermann —	Hemoglobin 98 per cent; red blood cells 4,900,000
Köplin, F.: Ztschr. f. klin. Med. **130**: 784-788, 1936	58	F	..	1:512	—	—	Hands, feet	—	—	..	Hemoglobin 54 per cent; red blood cells 2,080,000
Stratton, F.: Lancet **1**: 613-614 (May 5) 1943	62	F	..	1:256		—	Fingers	—	..	..	Hemoglobin 52 per cent; red blood cells, 2,500,000
Ginsberg [8]	34	M	W	1:2,048	+	—	—	—	+	Kahn —	Hemoglobin 45 per cent; red blood cells 1,360,000
Ernstene and Gardner [6]	38	M	W	1:1,280	—	—	Ears, nose, fingers	—	+	Kahn —; Wassermann —	Hemoglobin 10.5 Gm./100 cc.; red blood cells 3,800,000
Whittle, Lyell and Gorman [5a]	65	F	W	1:2,000,000	—	—	Hands, ears, nose	—	+	Kahn —; Wassermann —	+
Case 1	22	M	W	1:2,560	+	—	—	+	—	Wassermann —	Hemoglobin 15 Gm./100 cc.
Case 2	43	M	W	1:2,621,440	—	—	Nose, ears, fingers	—	+	—	Hemoglobin 10.5 Gm./100 cc.

* This patient had gangrene of the fingers.
† This patient had gangrene of the tips of the extremities.

malaise, increasingly severe nonproductive cough and dyspnea. There were moist rhonchi and fine rales in both lung fields. Cultures of the blood and sputum were negative. The white blood cell count was 6,500. On November 25, penicillin therapy was begun and the patient was placed in an oxygen tent. Within twelve hours, signs and symptoms of thrombophlebitis developed in the superficial veins of the right leg. It was noted that the oxygen tent was unusually chilly. The patient gradually recovered. At no time did he receive sulfonamide therapy. The cold hemagglutinin titers were 1:1,280 on November 27, 1:2,560 on December 2 and 1:640 on Jan 10, 1946.

The most curious cases are those in which transient or persistent high titers of cold hemagglutinins suddenly develop from no apparent cause. Case 2 is an example.

CASE 2.—M. L., an antique shop proprietor of 43, first experienced purplish blue mottling of the face, ears and fingers after exposure to cold in November 1944. The symptoms were followed by the passage of red urine. The patient's condition was diagnosed as "kidney disease," and he was treated with bed rest for two months. The symptoms reappeared when the patient was permitted to go out of doors but subsided during the following summer, only to reappear with the onset of cold weather. No jaundice was noted. There was no history of primary atypical pneumonia or of other viral infection. Physical examination was essentially noncontributory, except for acrocyanosis following exposure to the cold.

The patient was seen in the spring of 1946 by Dr. Alfred Vogl, of New York, who suspected the presence of cold hemagglutinins and referred him to me for further study.

On April 19, the patient's cold hemagglutination titer, as determined by Kettel's method,[2b] was 1:2,621,440 against both his own erythrocytes and type O red blood cells. Gross clumping was noted in a specimen of oxalated blood obtained at room temperature. The red cells remained clumped after being removed from the refrigerator and standing at room temperature (23 C.) for four hours. Dispersion of erythrocytes took place at incubator temperature.

The patient has been followed at the time of this report for a period of more than two years, during which he has remained in relatively good health. However, with exposure to cool weather there immediately develops bluish purple mottling of the ears, the cheeks, the tip of the nose and the fingers, accompanied with a mild sensation of tingling. About fifteen minutes later, red urine is passed.

The patient was urged to spend his winters in Florida, but this proved impractical; instead, he has consistently protected himself with warm gloves, stockings, etc., during cold weather.

Determinations of cold agglutination titer made at intervals during the two year period are listed in table 2. There has been a wavelike decline in titer with a tendency for the titer to be lowest during the summer. However, the thermal range remains so wide that blood counts are possible only when warm pipets and diluting fluid are used. A mild hypochromic anemia has developed.

On Feb. 10, 1948, salicylate therapy (5.2 Gm. of sodium salicylate daily in divided doses) was begun with the hope of blocking antigen-antibody reaction. At this time the cold agglutinin titer was 1:20,480. On February 17, it was 1:10,240 and the plasma salicylate level was 24.8 mg. per hundred cubic centi-

meters, as determined by the method of Brodie, Udenfriend and Coburn.[11] The patient continued to show symptoms of acrocyanosis for several days after the institution of therapy. Subsidence was difficult to evaluate because of a sudden spell of warm weather. Side effects of malaise, ringing in the ears, anorexia and constipation were pronounced. The dose of sodium salicylate was reduced to 3.6 Gm.

On February 24, the cold agglutinin titer had dropped to 1:2,560; the plasma salicylate level was 23.0 mg. Symptoms of anorexia, malaise and constipation persisted in a milder form.

On March 2, the cold agglutinin titer was 1:20,480. Clumping persisted for two hours at room temperature (25 C.) up to a dilution of 1:1,280. The plasma salicylate level was 17 mg. Since the improvement suggested earlier had not been maintained it was decided to abandon the use of the drug.

TABLE 2.—*Data in Case 2*

Date	Titer Cold Hemagglutinins	Plasma Salicylate Level, Mg./100 Cc.	Blood Counts
1946			
4/19	1:2,621,440	....	....
6/19	1:327,680	....	....
8/15	1:20,480	....	....
10/ 7	1:163,840	....	....
1947			
5/22	1:40,900	....	....
1948			
1/ 7	1:81,920	....	Hemoglobin 12.4 Gm./100 cc.
2/10	1:20,480	0	....
2/17	1:10,240	24.8	....
2/24	1:2,560	23.0	....
3/ 2	1:20,480	17.0	Hemoglobin 10.77 Gm./100 cc.; red blood cells 4,880,000; white blood cells 10,450
5/12	1:5,120	....	....
6/ 8	1:2,560	....	....

Subsequently the cold agglutinin titer fell spontaneously in a manner similar to that noted during previous summers.

COMMENT

It is apparent that the primary mechanism responsible for symptoms due to the presence of cold hemagglutinins is intravascular clumping of erythrocytes. The precipitating factor is presumably cold, whether due to chilling in an oxygen tent, low outdoor temperature or, possibly, transfusion with chilled blood. Stasis then occurs, most apparent in peripheral parts of the body. Patchy cyanosis appears but usually subsides when the patient is exposed to a warm temperature. However,

11. Brodie, B. B.; Udenfriend, S., and Coburn, A. F.: The Determination of Salicylic Acid in Plasma, J. Pharmacol. & Exper. Therap. **80**:114-117 (Jan.) 1944.

by then the tightly clumped erythrocytes have become more fragile than normal and tend to undergo hemolysis when subject to the trauma of circulation. Continued exposure to cold may cause the clumped erythrocytes to impede tissue oxygenation to the point where gangrene will develop in an extremity. This possibility should be considered in cases of bilateral gangrene in which exposure to cold alone has not been of a degree severe enough to produce this pathologic process. Local thrombosis of a deep part is more difficult to explain. The primary mechanism is probably the same. However, before erythrocyte dispersion can take place conversion of the clumped erythrocytes into actual thrombi has taken place with all the known effects of vascular occlusion.

Anemia of either of two types may occur. There may be moderate chronic anemia, such as the patient in case 2 exhibited. A probable explanation of this disorder is that repeated bouts of hemolysis are severe enough to raise the hemoglobin content of the blood to a level above the renal threshold. The blood-forming elements, mainly iron, are then lost to the body, and one may expect essentially an iron deficiency anemia which when uncomplicated results in a hypochromic microcytic blood picture. However, owing to the difficulty in making correct blood counts and hematocrit determinations in the presence of potent hemagglutinins, it is difficult or impossible to evaluate the character of the anemia present. Occasionally a hemolytic crisis takes place with a resultant severe anemia. Presumably, sudden severe chilling could initiate such a process, but such a history is rarely, if ever, noted.

Hemoglobinuria results whenever tubular absorption falls behind filtration rate. The red color of the urine voided by these patients is due to the presence of hemoglobin and not to that of free red blood cells.

It is a curious fact that the agglutination titer is not directly related to the type or degree of symptoms. Thermal range is doubtless important, especially in low titer serums.

Only a few cases with extremely high titers of cold hemagglutinins have been reported. Jessen and Bing [12] noted a macroscopic titer of 1 : 1,048,576 and a microscopic titer of 1 : 33,600,000 in the case of a woman of 69 with Banti's disease. Whittle and others [5a] reported an instance of a cold hemagglutinin titer of 1 : 2,000,000 in the case of a woman of 56 with symptoms suggesting Raynaud's disease and with occasional hemoglobinuria. A titer of 1 : 280,000 was observed by Favour [13] in a case of terminal myeloid leukemia. Erf [14] reported a

12. Jessen, C. U., and Bing, J.: Methods for Differentiating the Cause of Increased Sedimentation Rate, Acta med. Scandinav. **105**:287-300, 1940.

13. Favour, C. B.: Autohemagglutinins, J. Clin. Investigation **23**:891-897 (Nov.) 1944.

14. Erf, L. A.: A Note on the Stability of Cold Hemagglutinins, Am. J. Clin. Path. **15**:210-213 (May) 1945.

titer of 1 : 4,194,304 in the case of a man of 24 and one of 1 : 262,000 in that of a youth of 17; neither of the patients had acrocyanosis, thrombotic phenomena or hemoglobinuria. Erf also mentioned a personal communication from Dameshek regarding a patient with a cold hemagglutinin titer of 1 : 400,000, but no further details are given.

The use of salicylates was suggested by experimental work on animals and human beings reported in the literature. Swift [15] found that rabbits treated with sodium salicylate per os and at the same time immunized with intravenous injections of bacteria or sheep cells showed diminished complement-fixing antibodies, agglutinins and hemolysins when compared with controls. Anti-Rh-agglutinin formation in guinea pigs and rabbits is reduced when sodium salicylate is administered prior to and during immunization with rhesus monkey blood cells, according to the work of Homburger.[16] Jager and Nickerson [17] administered typhoid vaccine to patients receiving massive salicylate therapy; antibody formation was suppressed. Derick and his associates [18] postulated that arthritis from serum sickness was inhibited when circulating antibodies were kept at a low level by the use of antirheumatic drugs, such as neocinchophen and acetylsalicylic acid. The fact that urticaria was not prevented they attributed to the lack of effect of these drugs on sessile antibodies. Neither bacterial sensitivity to a streptococcus nucleoprotein fraction nor the Arthus phenomenon in rabbits was found to be altered by administration of salicylates (Fischel [19]). Coburn and Kapp [20] demonstrated inhibition of precipitate formation with sodium salicylate in a system containing crystalline egg albumin and its antibody. The immune system became progressively less sensitive to the action of salicylate as the excess of antibody became greater.

The effect of salicylates on the cold hemagglutinin titer in the patient in case 2 was negligible. Two explanations are suggested by the experimental studies of other authors: First, the salicylates were

15. Swift, H. F.: The Action of Sodium Salicylate upon the Formation of Immune Bodies, J. Exper. Med. **36**:735-760 (Dec.) 1922.

16. Homburger, F.: Sodium Salicylate Inhibiting Anti-Rh Immunization in Animals, Proc. Soc. Exper. Biol. & Med. **61**:101-102 (Feb.) 1946.

17. Jager, B. V., and Nickerson, M.: The Altered Response of Human Beings to the Intramuscular Administration of Typhoid Vaccine During Massive Salicylate Therapy, Am. J. Med. **3**:408-422 (Oct.) 1947.

18. Derick, C. L.; Hitchcock, C. H., and Swift, H. F.: The Effect of Anti-Rheumatic Drugs on the Arthritis and Immune Body Production in Serum Disease, J. Clin. Investigation **5**:427-440 (April) 1928.

19. Fischel, E. E.: The Effect of Salicylate and Tripelennamine Hydrochloride on the Arthus Reaction and on Bacterial Allergic Reaction, Proc. Soc. Exper. Biol. & Med. **66**:537-541 (Dec.) 1947.

20. Coburn, A. F., and Kapp, E. M.: Salicylate Effect on Immune Precipitates, J. Exper. Med. **77**:173-183 (Feb.) 1943.

given long after the beginning of antibody formation. Second, the action of salicylates is presumably less effective in the equivalence zone in the region where antibodies are in excess.

SUMMARY AND CONCLUSION

The symptoms of cold hemagglutination include paroxysmal acrocyanosis, thrombotic phenomena, hemoglobinuria and anemia. The primary factor producing most of these phenomena is apparently intravascular clumping initiated by exposure to cold.

Two cases are reported, 1 with very high titer cold hemagglutinins. Salicylate therapy had a negligible effect on the cold hemagglutinin titer and the symptoms in this case.

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ULCER OF THE PYLORIC RING

Report of Twenty Cases

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THE CLINICAL appraisal of ulcerating lesions within the grasp of the pyloric ring is difficult. Such ulcers are relatively rare in individual practice, and in the literature there are only a few widely scattered studies of their significance. The available articles were reviewed as a background for the present analysis of 20 cases of lesion of the pyloric ring for which satisfactory follow-up records were at hand.

SUMMARY OF THE LITERATURE

Butsch,[1] in 1935, summarized the experience at the Mayo Clinic with pyloric lesions. He found reports of 46 cases of pyloric ulcer in the surgical records there. Only 4 lesions had been accurately localized within the ring by roentgenologic studies. Ten lesions had been excised, and each had been found to be benign. In discussing this paper, Eusterman[2] said (1) that peptic ulcers of the ring are difficult to diagnose in spite of the fact that patients with such lesions usually come to medical attention after a relatively brief course; (2) that such ulcers usually run a stormy course with painful, spastic manifestations, and (3) that they tend to respond poorly to medical management.

Gutman and Hoffman[3] reported in 1935 that 41 ulcers of the pyloric ring had been treated in four years in the gastroenterologic service at the Salpétrière. This number represented about 1.5 per cent of all cases of peptic ulcers recorded in that service. The authors differentiated juxtapyloric ulcer, ulcer of the pyloric canal and ulcer of the base of the bulb. The differentiation was entirely roentgenologic, as they insisted that accurate localization within the canal was easier for the roentgenologist than for the surgeon. They described considerable variation in the position of the anterior pyloric vein, which is the surgical land-

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1. Butsch, W. L.: Ulcers of the Pyloric Ring, Proc. Staff Meet., Mayo Clin. **10**:435-437 (July 10) 1935.

2. Eusterman, G., in discussion on Butsch.[1]

3. Gutman, R. A., and Hoffman, R.: Ulcer of the Pyloric Canal, Arch. d. mal. de l'app. digestif. **25**:1009-1037 (Dec.) 1935.

mark of the sphincter. Sixteen patients in the series had had exploratory operations. In 6 instances, the surgeon had palpated the ulcer in the base of the bulb rather than in the ring.

Gutman and Hoffman asserted that ulcer of the pyloric ring gave rise to "the most variable symptomatology." In 14 of the 41 cases on which they had collected data, there was neither rhythmicity nor periodicity. In spite of the "exposed position" of the ulcer, bouts of pain were of short duration; however, they were of frequent occurrence. Eight patients had coexistent gastric ulcer; 9 had organic pyloric stric-

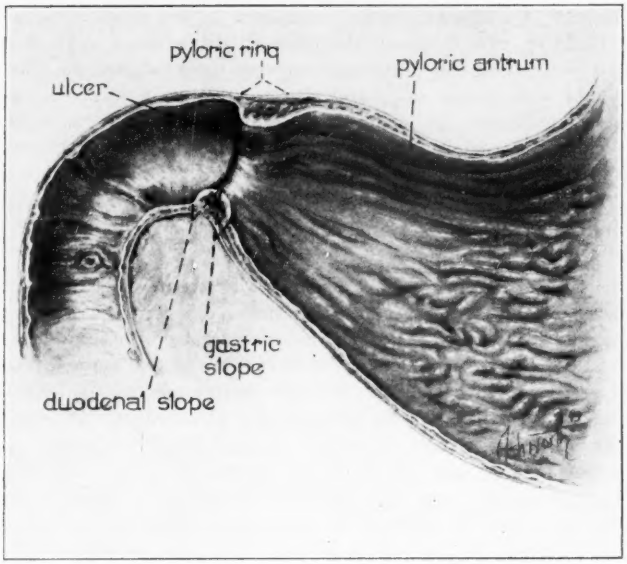

Diagram of the pyloric ring, showing typical location of ulcer.

ture, and 9 showed transitory or functional pyloric stricture. The authors recognized the potential malignancy of these lesions but reported no case in which there was a malignant lesion.

J. S. Horsley [4] in 1936 reported his operative findings in 12 cases of ulcer of the pyloric ring. Three ulcers had caused obstruction, 2 had bled and all were benign.

Jutras,[5] in 1936, discussed the roentgen diagnosis of pyloric ulcer and concluded that such diagnosis may be most difficult. He called atten-

4. Horsley, J. S.: Ulcer of the Pyloric Sphincter, Ann. Surg. **103**:738-746 (May) 1936.

5. Jutras, A.: Ulcers of the Pyloric Valve and Canal: Basis for Diagnosis, Union méd. du Canada **65**:660-670 (July) 1936.

tion to the false niches produced by the fan-shaped pyloric muscle of Cole. The author's classification for pyloric ulcer according to location, suggested for greater accuracy, was as follows:

Valve (ring)
- Gastric slope
- Orifice
- Duodenal slope

Canal (canal or prepyloric portion)
- Lesser curvature
- Greater curvature

In 1937, Garen and Bernay,[6] stimulated by the paper of Gutman and Hoffman, also discussed the roentgen diagnosis of ulcer of the pyloric ring. Their list of pertinent roentgen signs included the following: (1) niche in the ring (such defects are usually small—at most, "several" millimeters in length—and occur on the lesser curvature); (2) elongation and occasional angulation of the pyloric canal with spasm of the canal, and (3) deformity of the antrum adjacent to the ring with roughening of the base of the antrum.

In the experience of Garen and Bernay, stenosis rarely evolved from ulcer of the pyloric ring.

Jensen and Rivers,[7] in 1939, undertook a comparison of the clinical pictures in 25 cases of benign ulcer and in 25 of antral carcinoma impinging on the ring. They found indistinguishable histories in a third of these cases. After consideration of the histories as well as the roentgen findings, they concluded that one might be confused as to the exact nature of a lesion involving the pyloric ring in about 15 per cent of cases.

The next year, G. W. Horsley[8] reported 2 cases of benign ulcer of the pyloric sphincter, and Doub[9] studied 35 cases of true orificial and juxtapyloric ulcers. He excluded from consideration those cases in which "obvious carcinoma" of the antrum was observed on roentgen examination. In the selected group, there were 24 cases of peptic ulcer, 7 cases of antral carcinoma, 3 cases of antral gastritis and 1 case of gastric syphilis. Only 8 of these lesions involved the ring proper, and all 8 were benign peptic ulcers. But it is worthy of comment that 2 ulcers proved to be malignant at operation had been localized by the

6. Garen, C., and Bernay, P.: True Pyloric Ulcer, J. de méd. de Lyon **18**:453-456 (Aug. 20) 1937.

7. Jensen, R. M., and Rivers, A. B.: Carcinoma or Ulcer Involving the Pyloric Ring: Differential Diagnosis, Proc. Staff Meet., Mayo Clin. **14**:1-4 (Jan. 4) 1939.

8. Horsley, G. W.: Ulcers of the Pyloric Sphincter with Case Reports, Virginia M. Monthly **67**:29-32 (Jan.) 1940.

9. Doub, H. P.: Differential Diagnosis of Pyloric and Prepyloric Ulceration, Am. J. Roentgenol. **43**:826-831 (June) 1940.

roentgenologist within the ring, although at gross study they had appeared to be antral in position. Doub concluded that the greatest source of error in the clinical management of ulcers of the pyloric ring lay in the failure of anatomic diagnosis.

Smedal,[10] in 1942, reviewed possible sources of error in the roentgen diagnosis of lesions of the pyloric valve. He stated that accurate diagnosis of the anatomic position was possible and pointed out that the roentgenographic triad of deformity of the base of the cap, a poorly differentiated sphincter and antral spasm usually indicates the presence of an ulcer in the sphincter or on its duodenal slope. Visualization of a collar button–like crater penetrating the sphincter (usually on the side of the lesser curvature) made the diagnosis absolute. Of 10 cases reported by Smedal, the ulcer proved to be benign in 7. In the other 3 cases, the follow-up had not been long enough to prove benignancy.

Tanca Marengo [11] reported that there had been 3 cases of ulcer of the pyloric ring among 230 cases of ulcer of the upper gastrointestinal tract recorded over a ten year period. He, too, recognized the difficulty of accurate localization.

REVIEW OF CASES

The present series of 20 cases of ulcer of the pyloric ring was compiled after a review of all cases of peptic ulcer and carcinoma of the gastric antrum reported by a medical group over a twenty year period. Frank carcinomas of the pyloric antrum which had extended into the pyloric ring were excluded from the series.

There were ulcerating lesions of the stomach or duodenum in 2.8 per cent of all the cases studied by the group. One in every 200 such ulcerating lesions (0.5 per cent) proved to be in the pyloric ring.

The ulceration in the ring was demonstrated by direct visualization at operation in 15 cases and by roentgen examination alone in 5. The pathologic character of each of the 20 lesions was proved by an adequate biopsy, a prolonged follow-up or both. One of the 20 ulcers was malignant.

Fifteen patients were men, and 5 were women. Although their ages ranged from 32 to 77, 15 of the 20 patients were in the fifth or sixth decades.

The duration of symptoms at the time of diagnosis varied from three weeks to twenty years. The average was six and a half years.

In only 11 cases were the clinical symptoms characteristic of "peptic ulcer." Gaseous distress after eating was the predominant

10. Smedal, M. I.: Pyloric Ulcers, Radiology **39**:200-207 (Aug.) 1942.

11. Tanca Marengo, J.: Ulcers of the Pyloric Canal, An. Soc. méd.-quir d. Guayas **37**:1525-1529 (Jan.-March) 1946.

TABLE 1.—*Summaries of Reports of 20 Cases*

No.	Age and Sex of Patient	Duration of Symptoms at Diagnosis	Symptoms	Roentgen Observations	Therapy	Surgical and Pathologic Observations	Therapeutic Results	Duration of Follow-Up	Roentgen Evidence of Pyloric Obstruction	Free and Total Gastric Acidity at Diagnosis, Degrees (After Ewald Meal)
1	51 M	10 yr.	Periodic epigastric pain; free period over 6 months	Spastic antrum and bulb; pyloric ring deformed with crater; possible carcinoma	Symptomatic medical management	.....	Mild, recurrent dyspepsia; periodic heartburn	12 yr.	—	16; 32
2	53 M	9 yr.	Periodic epigastric pain; nausea relieved with sodium bicarbonate	Small crater at ring and induration of juxtapyloric walls, suggesting carcinoma	Gastric resection	Benign ulcer in pyloric ring	Patient asymptomatic	3 yr.	—	10; 19
3	68 M	1 yr.	Intermittent burning pain relieved by ingestion of food	Irregular pyloric margins with ulcer in ring; partial pyloric obstruction	Medical management (progressive Sippy treatment)	.....	Minor dyspepsia; no recurrent ulcer pain	7 yr.	+	..
4	55 M	2 yr.	2 episodes epigastric pain, each of 6 months' duration; 1 year free period between	Crater in ring or slightly behind pylorus; distortion of base of bulb	Gastric resection	Benign ulcer in pyloric ring	Patient asymptomatic	6 yr.	—	..
5	59 M	4 mo.	Severe gaseous distress and nausea; longest free period, 10 days	Large crater on pyloric sphincter	Gastric resection	Benign ulcer; crater on gastric slope of ring admitting fourth finger	Patient asymptomatic	15 yr.	—	61; 66
6	32 F	8 yr.	Irregular vague gaseous dyspepsia; occasional vomiting	Deformity in pylorus with ulcer defect	Gastric resection	Benign ulcer in pyloric ring (walls of ring thickened)	Postcibal gaseous dyspepsia relieved by belching	4 yr.	—	0; 23
7	49 M	10 yr.	Ulcer pain in periods to 4 months; occasional severe crisis of pain and vomiting	Spastic antrum and bulb	Gastric resection	Benign saddle ulcer in pyloric ring	Patient much improved; some gaseous dyspepsia	6 mo.	—	..
8	63 M	18 mo.	Ulcer pain and nausea with short free periods	Spastic bulb which could not be filled; spastic antrum	Gastric resection	Benign ulcer in pyloric ring with changes suggesting early adenocarcinoma	Patient asymptomatic; died of cerebrovascular accident; no malignant growth observed at autopsy	2½ yr.	+	..
9	65 M	3 yr.	Periodic epigastric pain; severe exacerbation of 3 months' duration just prior to diagnosis	Pylorus thickened and roughened; antrum spastic; crater appeared to be in base of bulb	Pylorectomy	Benign ulcer in pyloric ring and on its gastric slope	Patient asymptomatic	8 yr.	—	18; 35

10	51 M	3 wk.	Continuous nausea unrelieved by ingestion of food or sodium bicarbonate	Small crater in pyloric ring and duodenal slope	Gastrectomy	Benign florid ulcer in ring and on its gastric slope; second ulcer on posterior surface of ring	Dumping syndrome	6 yr.	—	0; 16
11	51 M	25 yr.*	Typical burning epigastric pain	Small crater determined to be in pyloric ring on side of lesser curvature on repeated studies; antral spasm and deformity of base of bulb	Medical management (progressive Sippy treatment)	.....	Patient asymptomatic	21 yr.	—	..
12	55 M	9 yr.	Recurrent gaseous distress and pressure on heart relieved by belching	Crater in ring; irregular pylorus; thickening of ring	Gastric resection	Benign ulcer, diameter 6 mm., on duodenal slope of ring; ring thickened	Patient asymptomatic	19 yr.	—	10; 21
13	48 F	4 yr.	Periodic hunger pain and gaseous distress associated with nausea, lasting to 3 months	Antral spasm; suggestion of crater in pylorus; pyloric obstruction	Gastric resection	Benign ulcer in pyloric ring	Postcibal gaseous distress in lower abdomen	26 yr.	+	68; 73
14	62 F	20 yr.	Recurrent epigastric distress with free periods lasting to 2 years	Antral spasm; irregular pyloric canal	Gastric resection	Tumor mass on posterior surface of ring with overlying ulcer that appeared benign on microscopic study	Patient died after 6 months of chronic nephritis; carcinoma in abdominal glands observed at autopsy	6 mo.	—	20; 28
15	55 F	4 yr.	Periodic hunger pain relieved with sodium bicarbonate; vomiting	Antral spasm with distorted base of bulb	Gastric resection	Large, indurated, benign ulcer in ring	Patient asymptomatic	22 yr.	—	49; 62
16	55 M	10 yr.	Recurrent ulcer distress responding temporarily to management; disabling pain and vomiting for 6 months prior to operation	Deformity of base of bulb with crater in ring	Gastric resection	Benign ulcer in ring	Patient asymptomatic	3 mo.	+	..
17	53 M	9 yr.	Periodic epigastric distress and fulness relieved with sodium bicarbonate; occasional nausea	Small crater at gastric side of pyloric ring	Subtotal gastrectomy	Ulcer, diameter 8 mm., at junction of pylorus and duodenum; active benign ulcer in ring	Patient asymptomatic	5 yr.	—	10; 19
18	77 F	8 yr.	Occasional distress 2 to 3 hr. after eating relieved with sodium bicarbonate	Small crater in pyloric ring; second ulcer on lesser curvature	Medical management (progressive Sippy treatment)	.....	Occasional localized pain and nausea	17 mo.	—	10; 22
19	45 F	10 yr.	Recurrent, severe vomiting relieved by ingestion of sodium bicarbonate or food; dull, diffuse epigastric pain, nonrhythmic during these episodes	Pylorospasm with ulcer involving pyloric ring; no retention at time of examination	Medical management	.....	Recurrent periodic vomiting	1½ yr.	+	62; 86
20	58 F	3 yr.	Monthly episodes epigastric pain and nausea of 3 to 4 days' duration; no relief with food	Persistent narrowing of pyloric canal; deformity of base of bulb	Gastrectomy	Benign ulcer, diameter 2.0 cm., of pyloric ring and its gastric slope	Patient asymptomatic	6 mo.	—	10; 23

* Recurrent ulcer pain and two hemorrhages occurred twenty-five years prior to recorded episode, which was of three months' duration.

symptom in 7 cases. Nausea was a complaint in 10. In 4, obstructive symptoms were present from time to time. However, in no case was there cicatricial pyloric stricture. Crisis-like pain and vomiting were present in 1 case.

Values for gastric acidity, when reported, tended to be in the lower normal range.

Accurate roentgen localization of crater of the pyloric ring was made in 12 cases. In 5 others, craters localized close to, but not in, the ring on roentgen examination proved at operation to be in the ring. Antral spasm was noted on fluoroscopic examination in 8 cases and spasm of the bulb in 7. In 2 cases, there was a significant, four hour, retention of barium sulfate.

Ten of the 15 patients who had been operated on reported themselves subsequently asymptomatic. Four reported nonincapacitating or minor postcibal fulness and distress. An annoying dumping syndrome characterized by postcibal distress, weakness, nausea and sweating developed in 1 case.

Of the 5 patients who elected medical management, 2 had recurrence of the ulcer distress on breaking the therapeutic routine. Two have gone seven and twelve years, respectively, at the time of writing without incapacitating or severe recurrence of the ulcer. One patient has remained free of recurrence for over twenty-one years.

COMMENT

It has been shown repeatedly that prepyloric ulcer tends, except in the presence of a second duodenal ulcer, to be malignant. This fact has colored the physician's diagnostic thinking about ulcer of the pyloric ring. In pointing out the high incidence of carcinoma in the prepyloric portion of the stomach, Holmes and Hampton[12] in 1932 carefully excluded from consideration those lesions involving the pyloric ring. Indeed, a review of the reported cases and the observations in the present series show that malignant ulcer within the ring is rare; benign ulcer is the rule. When direct visualization or roentgenographic examination shows a crater involving the pyloric ring, the chance of the lesion's being malignant is relatively small. Other factors may be considered in selecting the method of management.

The clinical value of this information, however, depends on the accurate localization of ulcers of the ring. Since no significant symptom complex characterizes localization in the ring, the roentgenographic evidence becomes of first importance. The demonstration of a crater in the ring should be attempted by fluoroscopic and roentgenographic

12. Holmes, G. W., and Hampton, A. O.: The Incidence of Carcinoma in Certain Chronic Ulcerating Lesions of the Stomach, J. A. M. A. **99**:905-908 (Sept. 10) 1932.

examination. In the absence of a demonstrable crater, the significant roentgenographic triad of antral spasm, a poorly differentiated ring and deformity of the bulb should be recognized. That such a complex indicates the presence of an ulcer in the ring or on its duodenal slope is borne out by the data in the present series. Seven of the patients showing this roentgenographic triad were found at operation to have craters of the ring. When the decision is difficult, a period of carefully controlled medical management may permit clarification of the roentgen signs.

The results of surgical therapy must be considered good. However, 5 of the 15 patients operated on continued to have dyspepsia, though in each case to a much lower degree than before the operation. It should be emphasized that their cases do not represent failures of medical management. Ten of the patients were operated on under the impression that ulcer of the ring was probably malignant, and 5 were operated on with the incorrect diagnosis of prepyloric ulcer. Only 3 of the 5 patients managed medically had results which could be considered good; these 3 patients have gone for many years at the time of this report without complications or noteworthy incapacity.

SUMMARY AND CONCLUSIONS

The literature concerning ulcer of the pyloric ring is reviewed.

Twenty cases of an ulcerating lesion in the pyloric ring are reported.

No characteristic symptom complex has emerged to permit accurate localization of an ulcer in the pyloric ring.

The accurate roentgenographic localization of many lesions of the ring is possible with the aid of Smedal's[10] roentgenographic triad (deformity of the base of the cap, a poorly differentiated sphincter and antral spasm).

The incidence of carcinoma in ulcer of the pyloric ring is relatively low.

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SPONTANEOUS RUPTURE OF SYPHILITIC SACCULAR ANEURYSMS OF THE ASCENDING AORTA INTO THE PERICARDIAL CAVITY, WITH HEMOPERICARDIUM

Report of Sudden Death in Twenty-Nine Cases

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THIS REPORT deals with sudden and unexpected natural death in 29 cases in which the cause of death was spontaneous rupture of a saccular aneurysm of the intrapericardial portion of the ascending aorta into the pericardial cavity, with resultant hemopericardium and cardiac tamponade.

The pathologist, in performing an autopsy, attempts to determine the cause of death. One of the least difficult diagnoses is that of a large hemorrhage into the pericardial cavity. If the pericardium is healthy, the hemorrhage may occur in various ways: (*a*) from spontaneous rupture of the heart wall, from chronic cardiac aneurysm or from necrosis of the myocardium after occlusion of a coronary artery; (*b*) from rupture of a dissecting aneurysm of the aorta into the pericardial cavity; (*c*) from an aneurysm of the otherwise normal coronary artery or of the pulmonary artery or from rupture of an atheromatous coronary artery; (*d*) from trauma, such as bullet and stab wounds of the pericardium and heart, traumatic cardiac rupture due to direct injury, bone fracture or compression; other forms of trauma, and (in true rupture) either internal pressure or tearing, and (*e*) from rupture of a syphilitic saccular aneurysm of the ascendnig aorta, lying within the pericardial cavity or eroding into the pericardial cavity.

SOURCE OF MATERIAL

The Office of the Chief Medical Examiner of the city of New York, from whose files these case records were selected, is called on to investigate approximately 16,000 deaths each year.[1] This figure represents about 20 per cent of all deaths occurring in the city of New York; of these, about 50 per cent are due to natural

From the Office of the Chief Medical Examiner, City of New York.

1. Annual Statistical Reports of the Office of the Chief Medical Examiner, New York.

causes. The law requires that sudden, unexpected or unusual deaths be reported to the medical examiner's office for investigation.[2] "Natural death" indicates that trauma played no part in the causation.

Autopsies were performed in only 16 per cent of natural deaths recorded, as compared with 25 per cent of all deaths.[1] The latter percentage was higher because of the mandatory performance of necropsy in violent or traumatic deaths.

Helpern and Rabson,[3] in a study of the records of the Office of the Chief Medical Examiner of 2,030 sudden and unexpected natural deaths in which an autopsy was performed in the Borough of Manhattan from Jan. 1, 1937, to June 30, 1943, noted that death was due to disorders of the heart and aorta in 912 cases (44.9 per cent). Syphilitic aortitis, complicated by aneurysm, occlusion of coronary ostiums or aortic valvular insufficiency, occurred in 107 cases, or 11.7 per cent of the deaths due to disorders of the heart and aorta and 5.3 per cent of the total of 2,030 deaths.

PATHOLOGY

The pathology of syphilitic aortitis has been described by various authors.[4] All were essentially in agreement as to the gross and microscopic appearance of the lesions in syphilitic aortitis.

The earliest lesions occur in the adventitia of the root of the aorta. About the vasa vasorum, a collection of round cells appears, including lymphocytes and plasma cells. Small miliary gummas may be formed. Obliterating endarteritis of the vasa vasorum takes place. Some of the vasa vasorum extend into the media, where their growth is associated with obliterating endarteritis, destruction of the elastic tissue, forma-

2. New York City Charter 1901, sect. 1570 and 1751, as added by L. 1915, ch. 284, sect. 2.

3. Helpern, M., and Rabson, M. S.: Sudden and Unexpected Natural Death—General Considerations and Statistics, New York State J. Med. **45**:1197, 1945.

4. (*a*) Leary, T.: Syphilitic Aortitis as a Cause of Sudden Death, New England J. Med. **223**:789, 1940. (*b*) Leary, T., and Wearn, J. T.: Two Cases of Complete Occlusion of Both Coronary Orifices, Am. Heart J. **5**:412, 1930. (*c*) Berk, L. H.: Cardiovascular Syphilis, New York State J. Med. **41**:223, 1941. (*d*) Martland, H. S.: Syphilis of the Aorta and Heart, Am. Heart J. **6**:1, 1930; (*e*) Pathology of Syphilis with Special Reference to the Development of Luetic Aortitis, Bull. New York Acad. Med. **8**:451, 1932. (*f*) McDonald, S., Jr.: Syphilitic Aortitis in Young Adults with Special Reference to a Congenital Etiology, Brit. J. Ven. Dis. **10**:183, 1934. (*g*) Saphir, O., and Scott, R. W.: Observations on One Hundred and Seven Cases of Syphilitic Aortic Insufficiency with Special Reference to Aortic Valve Areas, Myocardium and Branches of the Aorta, Am. Heart. J. **6**:56, 1930; (*h*) Involvement of the Aortic Valve in Syphilitic Aortitis, Am. J. Path. **3**:527, 1927. (*i*) Scott, R. W.: Syphilitic Aortic Insufficiency, Arch. Int. Med. **34**:645 (Nov.) 1924. (*j*) Warr, O. S.: Syphilis of the Heart and Aorta—A Report of One Hundred Cases with Autopsy Findings, South. M. J. **25**:711, 1932.

tion of gummas and development of fibroblastic tissue. As a result of the diffuse destruction of the media, the aorta dilates because the weakened, nonelastic aorta cannot resist the sustained intra-aortic pressure. If the destruction of the media is localized aneurysms may develop. These are saccular in the localized forms, but diffusely fusiform if the destruction is more extensive. Unless aortic insufficiency or atresia of the ostiums of the coronary vessels is present, an aneurysm has little effect on the heart. The intima becomes greatly thickened. The wall of the aorta, on cross section through the areas of syphilitic involvement, may be seen to be thickened.

The gross appearance of the syphilitic aorta is characteristic. The intima has lost its smooth appearance, showing irregular, longitudinal wrinkling, or "tree barking" the effect of the underlying areas of inflammatory fibrosis in the media, which causes the elevations and depressions seen in the intima. Thickened, pearl gray plaques are present, which in early lesions are sharply outlined, elevated and translucent. As the lesion becomes older these plaques tend to spread, so that the entire intimal surface becomes irregular, with pitting and scarring.

The root of the aorta at its origin is by far the commonest place of involvement, because of the rich supply of vasa vasorum in that region.[4b] Sites in order of decreasing frequency are the ascending aorta, the arch, the descending aorta and, last, the abdominal aorta.[5]

The earliest lesion that can be seen grossly is located just above the commissures distal to the attachment of the aortic cusps. The lesion is pearl gray, raised, has a sharp outline and, as Martland has described it,[4d,e] is roughly triangular, the base of the triangle pointing upward in the direction of the length of the aorta. The early plaque may be the only evidence of syphilis at autopsy, or, from such a plaque in the root, the process may spread horizontally so as to encircle completely the root of the aorta (this condition is sometimes called the girdle of Venus). The process may spread up the ascending aorta to the origins of the great vessels arising from the aortic arch, continuing up these vessels or causing a narrowing of their mouths. From the arch the process then may extend into the thoracic aorta.

Separation of the aortic commissures occurs when the syphilitic process in the root of the aorta continues downward, in the line of least resistance, between the attachments of the aortic cusps. In the commissure one may find a thickened, longitudinal, raised area separating the attachments of the cusps. As a result of the separation, dilation of

5. Willius, F. A.: Newer Concepts of Cardiovascular Syphilis, J. Tennessee M. A. **27**:494, 1934; Cardiac Clinics; Clinic on Syphilitic Aortitis with Aortic Insufficiency; Cardiac Hypertrophy with Congestive Failure, Proc. Staff Meet., Mayo Clin. **10**:505, 1935.

the aortic ring takes place, causing an aortic insufficiency. The free edges of the aortic cusps may be thickened and rolled; this is not primarily an organic change but, rather, a functional one, due to the mechanical effect of the aortic insufficiency. Just below the aortic cusps and on the posterior wall of the left ventricle are false valves due to endocardial reduplication, which, in turn, is a result of the passage of blood back into the left ventricle due to the aortic insufficiency. The syphilitic involvement at the root of the aorta may cause an increase in the circumference of the aorta, just above the free margins of the cusps. This dilatation may be sufficient to cause an insufficiency of the aortic ring, even though the syphilitic process has not extended downward to the commissures so as to separate the cusps. The aortic insufficiency, if it develops early, before dilatation of the aorta, may at times prevent the formation of aneurysm by relieving intra-aortic pressure. However, aortic insufficiency may occur after the development of aneurysmal dilatation of the aorta if the syphilitic process then extends down to the commissures.

Anatomically, it is of interest to note that the root of the aorta lies within the pericardial reflection. It is also to be noted that syphilis of the aorta occurs most commonly in the root of the aorta, which therefore is the region of oldest syphilitic involvement. The intrathoracic pressure is also greatest in the first part of the aorta. It is therefore not surprising to observe either a small saccular aneurysm which has ruptured into the pericardial cavity or a dissecting aneurysm which, unable to dissect upward because of the scarring of the media, ruptures through the adventitia and into the pericardial cavity. Either condition may lead to sudden death by causing tamponade.

The frequent coexistence of syphilis of the ascending aorta and atheromatosis has been noted by many pathologists. It is only in the older age groups that one finds arteriosclerotic changes in the ascending aorta, and these never progress to the extent to which they are found in syphilis. This is more than coincidence: Syphilis of the ascending aorta, if of sufficient duration, predisposes to associated atheromatosis, with its characteristic yellow plaques, hyaline and fatty atheromatous ulcers and calcification.[6]

REPORT OF CASES

CASE 1.—W. L., a white man aged 45, became ill at his place of employment and died in a few minutes, on July 5, 1938. Cause of death was spontaneous rupture of a saccular aortic aneurysm. Other findings were intrapericardial hemorrhage and syphilitic aortitis.

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6. Leary,[4a] Berk,[4c] Gordon, W. H.; Parker, F., Jr., and Weiss, S.: Gummatous Aotitis, Arch. Int. Med. **70**:396 (Sept.) 1942. Jensen, J.: Cardiovascular Syphilis, Urol. & Cutan. Rev. **46**:152, 1942. Smith, A. L. Mesaortitis: Its Pathology and Diagnosis, ibid. **46**:156, 1942.

Necropsy.—The heart was normal in size. The pericardial cavity was filled with blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible. The myocardium showed no lesions. The mouths of the coronary arteries were normal. On section, the coronary arteries presented only slight sclerosis. The ascending aorta showed a syphilitic process. On the posterior wall of the ascending aorta was a saccular aneurysm, measuring about 1¼ inches (3 cm.) in diameter and about 1 inch (2.5 cm.) in depth. The wall of the aneurysm was thinned out; a small perforation, ¼ inch (0.6 cm.) in diameter, was present at the lower part. The perforation opened directly into the pericardial cavity. The arch and the thoracic aorta revealed a syphilitic process.

Case 2.—W. R., a Negro aged 30, died Sept. 30, 1939. He had experienced severe pain early in the morning and died within a few minutes. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 350 Gm. The pericardial cavity was distended with a large amount of fresh clotted and fluid blood, which had caused a heart tamponade. The valves of the heart were normal and flexible. There was no evidence of aortic insufficiency. The cusps of the aortic valve were normal. The mouths of the coronary vessels were patent. The coronary arteries were observed to be normal on section. The myocardium showed no lesions. The aorta showed a chronic syphilitic process with wrinkling, puckering and thickening. Three quarters of an inch (0.8 cm.) above the posterior cusp of the aortic valve there was a saccular aneurysm, the mouth of which was 1¼ inches (3 cm.) in diameter; the cavity was 1 inch (2.5 cm.) in depth and was partially lined with soft, thrombotic material, and one small ⅛ inch (0.3 cm.) perforation was located ¾ inch (1.8 cm.) above the atrioventricular sulcus and ½ inch (1.2 cm.) to the left of the left atrial appendage. The rupture opened directly into the pericardial cavity.

Case 3.—H. G., a white man aged 35, died suddenly Nov. 9, 1939 while in the bathtub. His head was not submerged, and only a small amount of water was present in the tub. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta. Other findings were hemopericardium and chronic syphilitic aortitis. Results of Kline diagnostic and exclusion tests were positive.

Necropsy.—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart, including the aortic valve, were normal and flexible. The mouths of the coronary arteries were patent; on section, no lesions were observed. The myocardium was soft, light brown and free of lesions. There was a syphilitic process of the ascending aorta. A saccular aneurysm was situated ½ inch (1.2 cm.) above the left coronary cusp. The mouth of the aneurysm was 2 inches (5 cm.) in diameter and 2½ inches (6.2 cm.) in depth. The wall was pearl gray, with longitudinal wrinkling and some thrombus formation. At the lower part of the aneurysm was a small rupture, ⅛ inch (0.3 cm.) in diameter, opening directly into the pericardial cavity.

Case 4.—L. T., a Negro woman aged 36, was found lying dead on her bathroom floor, on Nov. 21, 1939. She had complained of gas and pains in the region of the heart. Cause of death was spontaneous rupture of a saccular aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 600 Gm. Considerable hypertrophy and some dilatation of the left ventricle were noted. The pericardial cavity was distended with fluid and clotted blood, which had compressed the heart. The valves of the heart, including the aortic valve, were normal and flexible. No separation of the commissures of the aortic valve had occurred. A chronic syphilitic process was present about the mouths of the coronary arteries, which, however, were not greatly narrowed. The coronary arteries showed moderate sclerosis on section. The myocadium presented a few scattered fibrous patches. The ascending aorta showed pearl gray plaques, with irregular thickening of the aortic wall. The syphilitic process extended to the arch of the aorta and several inches down the thoracic aorta. There was a saccular aneurysm of the ascending aorta about 1 inch (2.5 cm.) above the aortic cusps on the right anterolateral aspect. It was ¾ inch (1.8 cm.) in diameter and ½ inch (1.2 cm.) in depth; ¼ inch (0.6 cm.) rupture in the center opened directly into the pericardial cavity.

CASE 5.—X. C., a white man aged 78, died suddenly at his home on Feb. 1, 1939. He had been treated for syphilis for the past ten years and had had hoarseness and loss of voice. Cause of death was spontaneous rupture of a massive aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 500 Gm. The pericardial cavity was distended with fluid and clotted blood, which had completely surrounded and compressed the heart. The valves of the heart with the exception of the aortic and mitral valves were normal and flexible. Slight fibrous thickening of both mitral valve leaflets was present along the line of closure. The aortic valve cusps were also slightly thickened and were somewhat stiffened. There was no separation of the commissures of the aortic valve. The mouths of the coronary arteries were patent and not affected by the syphilitic aortitis. On section the coronary arteries showed a moderate grade of atherosclerosis, with eccentric displacement and narrowing of the lumen. Scattered throughout the myocardium of the left ventricle was a considerable amount of fibrosis.

On opening the aorta, a large saccular aneurysm was seen to involve the entire ascending aorta; it began about ⅜ inch (0.9 cm.) above the aortic valve and extended up to involve the top of the arch of the aorta. The aneurysm occupied a considerable portion of the medial part of the left side of the chest and was held by easily broken fibrous adhesions to the medial surface of the left lung. The lesion, which also bulged over to the right side of the chest, measured 6 inches (15 cm.) transversely, 5½ inches (13.8 cm.) vertically and 4 inches (10 cm.) in thickness. It had ruptured into the pericardial cavity through a small tear in the thinned-out wall of the anterior inferior portion of the aneurysm, the tear being ¾ inch (1.8 cm.) below the superior reflection of the pericardial sac, where it intercepted the ascending aorta. The inner wall of the aneurysm contained a large amount of laminated blood clot, which was rather soft and friable. The lining of the dilated aorta, which formed the aneurysmal sac, was the seat of advanced syphilitic aortitis, with characteristic puckering, scarring and plaque formation. There was considerable superimposed calcification of the ascending aorta. The syphilitic aortitis was also present in the descending aorta as far down as the bifurcation. The left recurrent laryngeal nerve was embedded in the fibrous tissue on the posterior surface of the aneurysm. The syphilitic aortitis extended up into the great vessels branching off the arch of the aorta.

CASE 6.—J. J., a white man aged 55, was found dead in bed in his rooming house, on April 15, 1939. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible. The mouths of the coronary arteries were patent. On section the coronary arteries were observed to be patent, showing only slight sclerosis. The myocardium appeared normal. A large aneurysm of the ascending aorta extended up to the aortic arch; the aneurysm was 5⅝ inches (14 cm.) in circumference. The ascending aorta and the lining of the aneurysm showed yellowish and pearl gray plaques; atheromatous plaques, a few of which showed superficial ulceration, were intermingled. A T-shaped rupture of the aneurysm was located just within the reflection of the pericardium on the aorta anteriorly.

CASE 7.—W. R., a Negro aged 43, had been in apparently good health but collapsed on the street and died almost immediately, on June 5, 1939. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 575 Gm. Hypertrophy and dilatation of the left ventricle were present. The pericardial cavity was filled with fluid and some clotted blood, which completely surrounded the heart. The aortic valve was dilated because of a separation of the commissures by thickened, pearl gray plaques, which extended upward and to each side of the commissures. The aorta was thickened by characteristic pearl gray plaques, with longitudinal wrinkling. Between the plaques were yellow sclerotic plaques and some calcification. The mouths of the coronary arteries were involved in the syphilitic process and were smaller than normal. On section the coronary arteries showed a moderate grade of sclerosis; the lumen was narrowed, but not obstructed. The myocardium showed a few fibrous patches. There was a small saccular aneurysm of the ascending aorta, located ½ inch (1.2 cm.) above the commissure separating the noncoronary from the right coronary cusp. The aneurysm, ½ inch (1.2 cm.) in diameter and ½ inch in depth, was thinned out; in its center was a perforation about ⅛ inch (0.3 cm.) in diameter, opening into the pericardial cavity. The rest of the aorta showed some sclerosis and a few pearl gray longitudinal plaques.

CASE 8.—S. B., a Negro aged 41, was found dead in his bed on June 25, 1939. According to relatives, he had complained of being ill shortly before his death. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were tamponade of the heart, chronic syphilitic aortitis and chronic rheumatic valvular disease, affecting the mitral and aortic valves. The results of Kline diagnostic and exclusion tests were positive.

Necropsy.—The heart weighed 500 Gm. Slight hypertrophy of the left ventricle was noted. The pericardial cavity was distended with 550 cc. of fluid and clotted blood, tamponading the heart. The tricuspid and pulmonary valves were normal. The leaflets of the mitral valve showed fibrous thickening, especially along the line of closure, with evidence of vascularization; slight thickening of the chordae tendineae had taken place. The cusps of the aortic valve were thickened, with small, ridgelike scars along the line of closure. The aortic ring was 3¼ inches

(8 cm.) in circumference. The ascending aorta, the arch and the descending aorta showed uneven thickening, puckering and wrinkling; a few small atheromatous plaques were intermingled. Thickening of the aorta had taken place along the commissures between the cusps, but the syphilitic process had not spread down so as to separate the commissures. A small saccular aneurysm was located ¼ inch (0.6 cm.) above the commissure between the right anterior and the posterior cusp; it was ⅜ inch (0.9 cm.) in diameter and ⅜ inch in depth, and its external surface was the adventitia on the anterior surface of the aorta, which was just adjacent to the appendage of the left atrium. A ⅛ inch (0.3 cm.) rupture, on the surface of the aneurysm, opened into the pericardial cavity. The mouths of the coronary arteries were patent except for a slight narrowing of the mouth of the right coronary artery. The coronary arteries showed a moderate amount of sclerosis. The myocardium appeared normal; on section, no lesions were observed.

Case 9.—L. S., a white man aged 43, died Jan. 30, 1941. He was said to have fallen suddenly to the ground while unloading bags of cement from a truck. He died almost immediately. Cause of death was spontaneous rupture of an aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 300 Gm. The pericardial cavity was distended with fluid and clotted blood. Above the pericardial sac was an aneurysm of the ascending aorta and the arch of the aorta. The dilatation began 1½ inches (3.7 cm.) above the aortic valves; it then formed a large saccular aneurysm of the aorta 2½ inches (6.2 cm.) in length. The aneurysm was thin walled and about the size of an orange; it lay behind the heart and was in contact with the pericardial sac, just above and posterior to the right atrium. The aneurysm had ruptured through a tear in the aorta, ½ inch (1.2 cm.) in diameter, and had torn a ½ inch opening in the pericardial cavity, so that from the inner surface of the pericardial cavity a direct communication had been established with the inner surface of the aneurysm. The cavity of the aneurysm, in addition to the syphilitic process, showed extensive atherosclerosis, with calcification in spots and some friable thrombus material. The remainder of the ascending aorta showed a syphilitic process combined with atheroma, which extended throughout the rest of the aorta, ending 3 inches (7.5 cm.) above the bifurcation of the abdominal aorta. The valves of the heart were normal and flexible. The aortic valve was normal. The mouths of the coronary arteries were not involved in the syphilitic process. The coronary arteries showed moderate atherosclerosis, but the lumen was patent throughout. The myocardium appeared to be normal and showed no lesions.

Case 10.—H. S., a Negro woman aged 42, became ill suddenly while traveling in a bus, collapsed and died in a few minutes, on Feb. 19, 1941. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, causing a complete tamponade of the heart. The valves of the heart were normal and flexible. The ascending aorta was the seat of a syphilitic process with pearl gray plaques and longitudinal wrinkling; the lesion did not, however, involve the mouths of the coronary arteries. On section the coronary arteries were observed to be normal. The myocardium showed no lesions. A saccular aneurysm of the ascending aorta was situated about ¾ inch

(1.8 cm.) above the aortic valves on the anterior surface, just to the right of the pulmonary artery. The aneurysm was 1 inch (2.5 cm.) in diameter; there was a ¼ inch (0.6 cm.) rupture in it, adjacent to the pulmonary artery.

CASE 11.—M. G., a Negro woman aged 38, died April 7, 1941. She collapsed while at home talking to members of her family and died in a short time. The family stated that she had not been ill before. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 370 Gm. The pericardial cavity was filled with fluid blood, which compressed the heart. The valves were normal and flexible. The ascending aorta showed a syphilitic aortitis, with pearl gray plaques and longitudinal wrinkling. The opening of the right coronary artery was almost completely obliterated by the syphilitic process; that of the left artery was only slightly involved, but was patent. The coronary arteries showed no lesions on section. The myocardium was normal. Situated between the right coronary and the noncoronary cusp, and about ½ inch (1.2 cm.) above the latter, was a small aneurysm, with thinned-out walls and measuring ¼ inch (0.6 cm.) in diameter, in the center of which was a ⅛ inch (0.3 cm.) perforation opening into the pericardial cavity.

CASE 12.—R. B., a Negro aged 35, died Jan. 5, 1942. He was known to be diabetic. He was found lying on the floor at his place of employment by a fellow employee. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which compressed the heart from all sides. The valves of the heart were normal and flexible. The mouths of the coronary arteries were only slightly encroached on by the syphilitic process in the aorta and were not narrowed. On section the coronary arteries showed no lesions. The myocardium was normal. The ascending aorta showed pearl gray plaques and longitudinal wrinkling. On the posterior wall of the aorta, about ¾ inch (1.8 cm.) above the right coronary and the noncoronary cusp, was a saccular aneurysm, 1 inch (2.5 cm.) in diameter; a small perforation, ⅛ inch (0.3 cm.) in diameter, was present in the depth of the aneurysm opening into the pericardial cavity.

CASE 13.—G. C., a Negro aged 43, was said to have had a heart attack on Jan. 12, 1942; he was treated by a physician, who advised him to stay in bed for a week. On January 15, while at work, he became ill. When an ambulance surgeon arrived, the patient was in coma, perspiring and breathing slowly. He came out of the coma and became maniacal, and the surgeon administered ¼ grain of morphine sulfate. The patient quieted down; while en route to the hospital his respiration again became slow, and he died in the ambulance. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta with rupture into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was enlarged. It was adherent to the chest wall by fibrous adhesions, especially near the conus arteriosus. The pericardial cavity was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible with the exception of the aortic valve, which showed some separation at all the commissures. There was a syphilitic process of the ascending aorta, which also encroached on the mouths of

the right and left coronary arteries, narrowing them. The coronary arteries showed a slight amount of sclerosis on section. A few fibrous patches were scattered throughout the myocardium. An aneurysm of the ascending aorta, beginning 1 inch (2.5 cm.) above the valves, was of considerable size and irregularly saccular. A point of rupture, about ½ inch (1.2 cm.) in length and situated at the junction of the aorta and the conus arteriosus, opened directly into the pericardial cavity.

CASE 15.—J. R., a white man aged 42, was found dead sitting on the stairs of his residence, on Feb. 17, 1942. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was enlarged. The pericardial cavity was distended with fluid and clotted blood, causing a tamponade of the heart. The valves of the heart were normal and flexible. The aortic valve appeared normal, although the aortic ring was somewhat dilated by the syphilitic process, which commenced just above the cusps. The mouths of both coronary arteries were encroached on and narrowed, but not occluded. An aneurysm of the ascending aorta, located just above the junction of the noncoronary cusp and the left coronary cusp, was about 1¾ inches (4.3 cm.) across the opening and about 1¾ inches in depth. It had thinned-out walls. There was a stellate perforation, ⅛ inch (0.3 cm.) in diameter, in the wall of the aneurysm, which opened directly into the pericardial cavity. The ascending aorta showed rugose, grayish and yellowish plaques and longitudinal wrinkling. On section the coronary arteries appeared moderately sclerotic, but they were patent throughout. The myocardium showed a few fibrous streaks.

CASE 16.—C. N., an Oriental man aged 45, was found lying dead on the floor of his residence on April 24, 1942. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, which had compressed the heart. The valves were normal and flexible. The mouths of the coronary arteries were of normal caliber. On section the coronary arteries were observed to be normal. The myocardium showed no lesions. The ascending aorta showed pearl gray plaques with longitudinal wrinkling. There was a large saccular aneurysm of the ascending aorta, which had emerged from the pericardial sac. Near the point of emergence of the aorta, the aneurysm had eroded back into the pericardial cavity, into which it had ruptured directly.

CASE 17.—E. Q., a Negro woman aged 49, collapsed while working as a laundress and died almost at once, on June 9, 1942. Her family stated that she had previously been in good health. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 300 Gm. The pericardial sac was distended by fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart, including the aortic valve, were normal and flexible. There was slight separation of the commissure between the posterior and the right coronary cusp. The mouths of the coronary arteries were not involved. On section the coronary arteries were seen to be normal and patent. The myocardium showed no lesions. The intimal lining of the ascending aorta was extensively wrinkled, presenting a typical "tree bark" appearance, with pearl gray plaques.

The syphilitic process extended as far up as the isthmus of the aorta. There was a small saccular aneurysm of the ascending aorta; its lower margin was situated ¼ inch (0.6 cm.) above the commissure between the posterior and the right anterior cusp. The aneurysm lay just adjacent to, and was overlapped by, the left atrial appendage. An ⅛ inch (0.3 cm.) perforation of the aneurysm was situated ¾ inch (1.8 cm.) above the sulcus, between the aorta and the right ventricle and ruptured directly into the pericardial cavity. The aneurysm was 1 inch (2.5 cm.) in diameter, was circular and had ½ inch (1.2 cm.) opening in the ascending aorta.

Case 18.—L. B., a Negro aged 38, was found lying dead in his bunk aboard a steamship on Dec. 9, 1942. Cause of death was spontaneous rupture of a small saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 500 Gm. and showed hypertrophy of the left ventricle. The pericardial sac was distended with clotted blood, causing a tamponade of the heart. The valves of the heart were normal and flexible. There was no separation of the commissures of the aortic cusps. There was slight dilatation of the aortic ring, which was 3 inches (7.5 cm.) in circumference. The mouths of the coronary arteries were patent. The syphilitic aortitis did not encroach on the aortic valve or on the mouths of the coronary arteries. The coronary vessels showed slight atherosclerosis. The myocardium was brown and showed no lesions. The ascending aorta, the arch and the descending aorta, almost to the diaphragm, presented a characteristic wrinkled, puckered and scarred appearance resembling the bark of a tree, with pearl gray plaques. There was a small saccular aneurysm just above the left anterior cusp of the aortic valve; it was ⅝ inch (1.5 cm.) in diameter. A small rupture of the aneurysm, ⅛ inch (0.3 cm.) in diameter, was situated between the commissure of the posterior and left anterior cusp and the mouth of the left coronary artery; it entered the pericardial cavity ½ inch (1.2 cm.) above the left atrial appendage, on the posterior surface of the ascending aorta.

Case 19.—W. B., a Negro aged 47, was suddenly taken ill, collapsed and died on a sidewalk, on Jan. 27, 1943. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 400 Gm. The pericardial sac was distended with clotted blood, causing a complete tamponade of the heart. The valves of the heart were normal and flexible. There was no separation of the commissures of the aortic cusps. The ascending aorta showed a syphilitic process with pearl gray plaques, a "tree bark" appearance and longitudinal wrinkling; this process extended through the entire aorta to the descending aorta. A saccular aneurysm of the ascending aorta located ¾ inch (1.8 cm.) above the cusps and measuring 1 inch (2.5 cm.) in diameter, contained a ¼ inch (0.6 cm.) rupture in its center, opening directly into the pericardial cavity. The mouths of the coronary arteries were patent and were not encroached on by the syphilitic process. On section the coronary arteries showed slight sclerosis, but no obstruction. The myocardium showed no lesions.

Case 20.—A. K., a white man aged 65 years, was found lying dead on the floor of the bathroom at his residence, on Aug. 2, 1943. Cause of death was spontaneous rupture of a large saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The valves were normal and flexible. The pericardial sac was distended with fluid and clotted blood, which had caused a tamponade of the heart. A large saccular aneurysm of the ascending aorta had eroded the posterior surface of the manubrium and the upper part of the body of the sternum. This aneurysm filled the superior mediastinum; it was 4½ inches (11.2 cm.) in diameter and lined with laminated clot, and its wall was calcified. A rupture ½ inch (1.2 cm.) in diameter, in the intrapericardial portion of the ascending aorta, opened directly into the pericardial sac. The syphilitic process encroached on, but did not narrow, the mouths of the coronary arteries. On section the coronary arteries showed slight sclerosis, but the myocardium showed no lesions.

CASE 21.—L. A., a Negro woman aged 38, died Dec. 14, 1943. She was found dead on the floor of her apartment by her husband, who stated that she had not been ill before. Cause of death was spontaneous rupture of a saccular aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 440 Gm. The pericardial cavity was filled with fluid and clotted blood, completely compressing the heart. The valves of the heart were normal and flexible. The mouths of the coronary arteries were slightly encroached on by the syphilitic process. The coronary arteries were normal on section. The myocardium showed no lesions. The ascending aorta showed a syphilitic process with "tree bark" appearance and pearl gray plaques. Three aneurysms of the ascending aorta were located just above the aortic valve and were from about ¼ inch (0.6 cm.) to 1 inch (2.5 cm.) in diameter. The largest showed 1 mm. perforation, located in its upper portion and opening directly into the pericardial cavity.

CASE 22.—An unknown Negro, about 38 years of age, collapsed on the street and died in a few minutes, on March 3, 1944. Cause of death was spontaneous rupture of a large saccular aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was not enlarged. The pericardial sac was distended with fluid and clotted blood, which had caused a tamponade of the heart. The valves of the heart were normal and flexible. The aortic valve cusps were not encroached on by the syphilitic aortitis, nor were the mouths of the coronary arteries. The coronary arteries showed no lesions on section. The myocardium was normal. The ascending aorta was slightly dilated. The wall was thickened and the intimal surface somewhat corrugated. An extensively scarred and thickened area lay in the ascending aorta, just above the commissure between the right and the left anterior cusp. This wrinkled, corrugated plaque was also somewhat calcified. There were wrinkling and corrugation of the aorta just above the posterior cusp. The remainder of the ascending aorta was fairly smooth, although thickened, and the adventitia was definitely thickened and fibrous. In the arch of the aorta was a 1⅝ inch (4 cm.) saccular aneurysm, directed upward and backward against the anterior surface of the trachea and extending up into the orifice of the right innominate artery. The aneurysm had a small sacculation, which was separated from the larger one by a fairly broad ridge, running upward in the fold of the arch. The smaller sac was ¾ inch (1.8 cm.) in diameter and opened into the angle between the pericardial reflection and the anterior surface of the ascending aorta; a rupture had occurred, connecting the aneurysm directly with the pericardial cavity.

CASE 23.—R. G., a Negro aged 39, had apparently always been in good health. Suddenly, while in the presence of friends, on March 22, 1944, he began to gasp for air, but made no other complaints. He died in a few minutes. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were cardiac compression and syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was distended with fluid and clotted blood, causing a tamponade of the heart. The valves were normal and flexible. The mouths of the coronary arteries were patent. The coronary arteries showed no lesions on section. The myocardium presented no lesions. The ascending aorta showed pearl gray plaques with longitudinal wrinkling. An aneurysm had arisen 1 inch (2.5 cm.) above the aortic cusps. It was about 1½ inches (3.7 cm.) in diameter and occupied the right side of the ascending aorta. In its depth it had a ¼ inch (0.6 cm.) perforation, which opened directly into the pericardial cavity.

CASE 24.—L. D., a white man aged 65, was found lying dead in the doorway of his residence, on April 11, 1944. Cause of death was spontaneous rupture of an aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was moderately enlarged. The pericardial cavity was filled with fluid and clotted blood, which completely compressed the heart. The valves on the right side were normal. The aortic valve showed some sclerosis at the base of the cusps; there was no separation of the commissures. The mouths of the coronary arteries were patent and were not encroached on. On section the coronary arteries showed a moderate degree of sclerosis; the lumens were somewhat narrowed, although no obstruction was noted. The myocardium showed patchy distribution of fibrous streakings. The ascending aorta above the aortic valves presented the appearance of "tree bark" with pearl gray plaques intermingled with yellowish plaques, many of which were calcified. About 1 inch (2.5 cm.) above the aortic valve was an aneurysm 2 inches (5 cm.) in length and 1 inch (2.5 cm.) in depth; this lesion had ruptured, through an opening ¼ inch (0.6 cm.) in diameter, into the pericardial cavity.

CASE 25.—J. S., a Negro aged 36, had been ill for five days with pain in the precordial region, radiating to his back and associated with dyspnea. The attending physician had diagnosed the condition as spontaneous pneumothorax of the right side. The patient was apparently doing well when, on May 19, 1944, he went outdoors. On his return he complained of feeling bad, became extremely dyspneic and fell to the floor. He was helped to bed but died in about fifteen minutes. Cause of death was spontaneous rupture of an aneurysm of the ascending aorta, with rupture into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart weighed 700 Gm. The pericardial cavity was greatly distended with fluid and clotted blood. The valves of the heart were normal and flexible. The aortic valve cusps were thin and transparent. The commissures were not widened. The aortic ring was 7.2 cm. in diameter. The ostium of the right coronary artery was slightly narrowed by the syphilitic process. The ostium of the left coronary artery was of normal caliber. On section the coronary arteries showed minimal atheromatous changes, but they were patent throughout. The myocardium was pale and flabby, but no lesions were visible on section. The entire ascending and transverse portions of the aorta, and a part of the descending aorta, showed a pronounced "pig skin" appearance of the intima, with pearly plaques. In the ascending portion of the aorta was a saccular aneurysm, with an

opening into the aorta 4.5 cm. in diameter. Attached to the depth of the aneurysm was soft thrombus and on the anterior portion of this aneurysm, just below the reflection of the pericardium, a rupture 1 cm. in diameter, opened directly into the pericardial cavity.

No pneumothorax was present. Both lungs contained air and showed edema and congestion.

CASE 26.—J. J., a white man aged 63, was suddenly taken ill, in a restaurant where he was employed, and died in a few minutes, on Sept. 7, 1944. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was filled with fluid and clotted blood, compressing the heart from all sides. The valves were normal and flexible. The mouths of the coronary arteries were not encroached on; they were of normal caliber. On section the coronary arteries showed a moderate grade of sclerosis, but no obstructions. The myocardium showed only an occasional fibrous streak. There was a syphilitic process of the ascending aorta, with pearly gray plaques intermingled with yellow ones, the latter showing calcification. An aneurysm of the ascending aorta, ¾ inch (1.8 cm.) in diameter, was situated at the aortic arch near its junction with the pericardial reflection. A 3/16 inch (0.45 cm.) perforation opened directly into the pericardial cavity.

CASE 27.—O. S., a white man aged 40, became ill in a hotel lobby and died in a short time., on Sept. 21, 1944. Cause of death was spontaneous rupture of an aortic aneurysm into the pericardial sac. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was filled with fluid and clotted blood, which had surrounded and compressed the heart. The valves were normal and flexible. The mouths of the coronary arteries were narrowed by the syphilitic process. The coronary arteries showed no lesions on section, nor did the myocardium. The ascending aorta showed rugose, pearly white plaques, intermixed with yellowish areas of calcification. There were two small aneurysms of the ascending aorta. One, about 1 inch (2.5 cm.) in diameter, was situated just above the right coronary cusp; the other, ¾ inch (1.8 cm.) in diameter, was 1 inch above the posterior cusp. The wall of the latter aneurysm was very thin; a rupture in its depth, ⅛ inch (0.3 cm.) in diameter, opened directly into the pericardial cavity.

CASE 28.—D. S., a Negro girl aged 17, was about eight months pregnant; while walking on the street with her mother she collapsed and died, on Sept. 24, 1945. Cause of death was spontaneous rupture of a small saccular aneurysm of the aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was completely filled with fluid and clotted blood. The valves of the heart were normal and flexible. There was no separation of the commissures. The mouths of the coronary arteries were patent and of normal caliber. The coronary arteries showed no lesions on section. The myocardium was normal. The aorta was thin walled and showed no lesions except a small aneurysm, about ¾ inch (1.8 cm.) in diameter and situated over the right coronary cusp. The wall of the aneurysm showed pearl gray plaques and longitudinal wrinkling. A small vertical rupture, ¼ inch (0.6 cm.), at the upper end of the aneurysm opened directly into the pericardial cavity.

CASE 29.—N. L., a Negro aged 50, was found lying dead on a sidewalk, on Nov. 5, 1945. Cause of death was spontaneous rupture of an aneurysm of the ascending aorta into the pericardial cavity. Other findings were hemopericardium and chronic syphilitic aortitis.

Necropsy.—The heart was normal in size. The pericardial cavity was filled with fluid and clotted blood, compressing the heart. The valves were normal and flexible. The mouths of the coronary arteries were of normal caliber. On section the coronary arteries showed a slight amount of sclerosis but no obstructions to the lumen. The myocardium showed no lesions. The ascending aorta showed pearly white plaques and presented a "tree bark" appearance. An aneurysm, 1 inch (2.5 cm.) in diameter, at the upper end of the ascending aorta, had thin walls; a soft thrombus was present in its depths. A rupture about ¼ inch (0.6 cm.) in diameter, located on the posterior surface of the aneurysm near the left atrium, opened directly into the pericardial cavity.

SIGNIFICANT FACTORS

In all the cases reported with the exception of cases 9 and 16 an aneurysm of the ascending aorta, saccular in type, had ruptured directly into the pericardial cavity. Necropsy in cases 9 and 16 showed large saccular aneurysms which were situated outside the pericardial cavity but had eroded through its lining, so that when they ruptured the opening communicated directly with the pericardial cavity, causing death by tamponade of the heart.

The aneurysms reported in this series were as a rule small and had thinned-out walls. Intra-aortic pressure is greatest in the ascending aorta; this factor, combined with the weakening of the wall of the aorta due to the syphilitic process, finally resulted in the blowing out of the aneurysm. It is interesting to note that only in cases 21 and 27 was there more than one aneurysm. A large aneurysm was present in cases 5, 6, 9, 13, 16, 20, 22 and 24, a total of 8 cases among the 29 reported in which the aneurysm was large enough to have been diagnosed ante mortem.

Age.—The youngest person in this series was the 17 year old Negro girl in case 28. This case was most interesting in that the small ruptured saccular aneurysm was the only evidence of syphilis at necropsy.

Six persons in the series were 50 years of age or more. The oldest in the series was 78 (case 5). A large massive aneurysm was found in this case, as was sclerosis of the cusps of the aortic and mitral valves; syphilis, then, was of long standing, at least ten years and perhaps longer, according to the history. Large, massive aneurysms were also present in cases 6, 20 and 24, while small aneurysms were noted in cases 26 and 29. One might infer, therefore, that in the older groups the syphilitic process is also older and that therefore aneurysms are larger when they finally rupture into the pericardial cavity. Sclerosis of the cusps of the aortic and mitral valves was also present in case 24.

Most of the deaths were of persons in the fourth or fifth decade of life.

Sex and Color.—Twenty-three men and 6 women are included in this series. This bears out the observation that aneurysm is more likely to develop in men, as has been shown in other studies.

Eleven patients in this series were of the white race, 17 were Negroes and 1 was of the yellow race. This represents a higher percentage of white patients than is usual for syphilitic cardiovalvular disease.

Size of the Heart.—The heart was of normal size in 20 cases, as compared with 9 in which enlargement was present. Aortic insufficiency due to separation of the commissures was noted in cases 7 and 13. Necropsy in cases 15, 18 and 25 showed normal cusps of the aortic valves and no separation of the commissures but definite dilatation of the aortic ring, due to the supravalvular syphilitic sclerosis, with resultant increase in the circumference of the aortic ring. In case 8 the enlargement was probably due to associated rheumatic valvulitis of the mitral and aortic valves. Case 24 was that of a man aged 65 with sclerosis of the mitral and aortic valves; in this case and in case 5, in which the man was 78, the process was probably due to arteriosclerosis with calcification of the aortic and mitral valves.

In cases 4 and 21 no explanation could be found for the enlargement of the heart.

Aortic Valve.—The aortic valves in most cases were flexible, and there was no separation of the commissures. The exceptions have already been mentioned.

Mouths of the Coronary Arteries.—In 19 cases no involvement of the mouths of the coronary arteries was recorded; in 10 cases some encroachment on both mouths was found. However, in no case had complete atresia of the mouths occurred.

COMMENT

The ascending aorta is about 5 cm. in length.[6a] It commences at the upper part of the base of the left ventricle and passes obliquely upward, forward and to the right in the direction of the heart's axis, describing a slight curve in its course. At the union of the ascending aorta with the aortic arch, the caliber of the vessel is increased, owing to a bulging of its right wall. The ascending aorta is contained within the pericardium and is enclosed in a tube of the serous membrane common to it and the pulmonary artery. The ascending aorta is covered at its commencement by the infundibulum of the right ventricle, the trunk of the pulmonary artery and the right atrium; posteriorly, it rests on

6a. Gray, H.: Anatomy of the Human Body, ed. 25, Philadelphia, Lea & Febiger, 1948.

the left atrium, the right pulmonary artery and the right bronchus. On the right side it is in juxtaposition with the superior vena cava and the right atrium, the former lying partly behind it; on the left side it is in juxtaposition with the pulmonary artery.

From the anatomic location of the ascending aorta it may be seen that aneurysms along the course of this vessel may rupture into the right atrium, the right ventricle, the conus arteriosus, the pulmonary artery, the superior vena cava, the left atrium, the right bronchus or, more commonly, directly into the pericardial cavity.

Herrmann and Schofield [7] recently reported on the syndrome of rupture of an aneurysm of the aortic root into the right atrium. Schwab and Sanders [8] and others [9] reported on aortic aneurysms rupturing into the conus arteriosus of the right ventricle. Scott [10] and Porter [11] reviewed the literature and reported on the syndrome of rupture of an aortic aneurysm into the pulmonary artery. Armstrong, Coggin and Hendrickson [12] reviewed the syndrome of rupture of an aortic aneurysm into the superior vena cava.

According to Kampmeier [13] and to Brindley and Schwab,[14] more than 50 per cent of deaths in persons with aortic aneurysm were due to rupture of the aneurysm. The usual sites of the rupture were in the left pleural cavity, the esophagus, the right pleural cavity, the vena cava, the left main bronchus and the pericardial cavity.

In the present series 27 deaths were due to rupture of the ascending aorta in that part which lies within the pericardial reflection, called the

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7. Herrmann, G. R., and Schofield, N. D.: The Syndrome of Rupture of Aortic Root or Sinus of Valsalva Aneurysm into the Right Atrium, Am. Heart J. **34**:87, 1947.

8. Schwab, E. H., and Sanders, C. B.: Aortic Aneurysm Rupturing into the Conus Arteriosus of the Right Ventricle, Am. J. M. Sc. **182**:208, 1931.

9. Tompkins, R. D.: Aneurysm of the Left Aortic Sinus of Valsalva with Rupture into the Right Ventricle (Intravitam Diagnosis), M. Bull. Vet. Admin. **18**:173, 1941. Harris, W. H., Jr., and Shattenberg, A. J.: Aneurysm of Aorta Rupturing into the Right Ventricle, Ann. Int. Med. **20**:961, 1944.

10. Scott, R. W.: Aortic Aneurysm Rupturing in the Pulmonary Artery, J. A. M. A. **82**:1417 (May 3) 1924.

11. Porter, W. B.: The Syndrome of Rupture of an Aortic Aneurysm into the Pulmonary Artery, Am. Heart J. **23**:468, 1944.

12. Armstrong, E. L.; Coggin, C. B., and Hendrickson, H. S.: Spontaneous Arteriovenous Aneurysms of the Thorax: A Review of the Literature with a Report of Two Cases, Arch. Int. Med. **58**:298 (Feb.) 1939.

13. Kampmeier, R. H.: Saccular Aneurysm of the Thoracic Aorta: A Clinical Study of Six Hundred and Thirty-Three Cases, Ann. Int. Med. **12**:624, 1938.

14. Brindley, P., and Schwab, E. H.: Aneurysms of the Aorta with a Summary of Pathologic Findings in One Hundred Cases of Autopsy, Texas State J. Med. **25**: 757, 1930.

pericardial cavity or sac. In 2 cases death was due to aneurysms which were outside the pericardial reflection but which had eroded into the pericardial cavity.

Death in this condition is usually sudden, occurring in a few minutes after the rupture into the pericardial cavity. Death ensues from the collection of blood in the pericardium and the tension it causes, whether by compression of the heart and the consequent prevention of diastolic expansion, or by prevention of the emptying of the cavae in the atria.

Syphilitic involvement of the aortic valves and the mouths of the coronary arteries is not as a rule associated with pure saccular aneurysms of the aorta. In the present series saccular aneurysms of the ascending aorta were as a rule associated with normal aortic valves, normal size of the heart and little encroachment on the mouths of the coronary arteries.

If these facts are correlated, it becomes apparent that saccular aneurysms of the ascending aorta may exist without the patient's presenting any symptoms or physical signs of the disease process of the ascending aorta. Only when an aortic insufficiency, atresia of the mouths of the coronary arteries or an aneurysm large enough to cause pressure symptoms or to be detected by fluoroscopic roentgenographic examination is present can the diagnosis of syphilis of the cardiovascular system be made.

The fact is stressed that the possibility of small saccular aneurysms of the ascending aorta lying within the pericardial cavity should be considered in all cases in which syphilitic cardiovascular involvement is considered because of other diagnostic findings.

SUMMARY

Twenty-nine cases of spontaneous rupture of a syphilitic aneurysm of the ascending aorta into the pericardial cavity, with resultant hemopericardium and tamponade of the heart, causing sudden death, are presented.

It is difficult to diagnose this condition ante mortem because it is not as a rule associated with aortic insufficiency, enlargement of the heart or atresia of the mouths of the coronary arteries.

Twenty-three men and 6 women, or 11 white persons and 17 Negroes, are included in the series.

The youngest person to die was 17 years of age, the oldest, 78.

Anatomically, syphilitic aneurysms of the ascending aorta may rupture into the right atrium, the right ventricle, the conus arteriosus, the pulmonary artery, the superior vena cava, the left atrium, the right bronchus or, as in this series, directly into the pericardial cavity from those portions of the ascending aorta which are not contiguous to any of the structures.

2327 Grand Concourse (53).

DISSECTING ANEURYSMS OF THE AORTA

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REPEATED attempts have been made to ascertain the underlying etiologic factors in idiopathic cystic necrosis of the aorta since it was first described by Gsell [1] and by Erdheim.[2] Workers have pursued several courses, among which have been the morphologic and the experimental. Among the former, the work of Erdheim is still fundamental and outstanding. He noted specifically the absence of vasa vasorum at the site of rupture in those instances in which the aorta showed the typical picture of medial necrosis. In other cases, he observed some degree of hyalinization. Despite his observations and the later work of Wiese,[3] he stated the belief that the vasa vasorum did not play a role in the production of medionecrosis of the aorta. He favored the idea of some form of hyperadrenalism as the possible etiologic factor. Later workers [4] noted alterations of the vasa vasorum.

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1. Gsell, O.: Wandnekrosen der Aorta als selbständige Erkrankung und ihre Beziehung zur Spontanruptur, Virchows Arch. f. path. Anat. **270**:1-36, 1928.

2. Erdheim, J.: Medionecrosis aortae idiopathica, Virchows Arch. f. path. Anat. **273**:454-479, 1929; Medionecrosis aortae idiopathica cystica, ibid, **276**:187-229, 1930.

3. Weise, W.: Medianekrosen, eine Untersuchung am laufenden Sektionsmaterial, Beitr. z. path. Anat. u. z. allg. Path. **93**:238-278, 1934.

4. (*a*) Moritz, A. R.: Medionecrosis aortae idiopathica cystica, Am. J. Path. **8**:717-734, 1932. (*b*) Rottino, A.: Medial Degeneration of the Aorta as Seen in Twelve Cases of Dissecting Aneurysm, Arch. Path. **28**:1-10 (July) 1939; (*c*) Medial Degeneration in Nonruptured Aorta Appearing Syphilitic Macroscopically, ibid. **27**:320-327 (Feb.) 1939; (*d*) Medial Degeneration of the Aorta: Study of Two Hundred and Ten Routine Autopsy Specimens by a Serial Block Method, ibid. **28**:337-385 (Sept.) 1939. (*e*) Rottino, A., and Poppiti, R.: Intimal Changes in Medial Degeneration of the Aorta, ibid. **36**:201-205 (Aug.) 1943.

Attempts to reproduce the lesion in rabbits by some form of injury to the vasa in the adventitia of the descending aorta or of the peripheral arteries have been made.[5] Other methods have included the injection of such drugs as epinephrine [6] and histamine [7] and the production of experimental shock. The work of one of us (J. G. S.),[5] in which necrosis of the media of the aorta in dogs was produced by coagulation of the adventitia of the ascending aorta, demonstrated the importance of the nutrition of the aorta by way of the vasorum. That study suggested to us that we review, with particular reference to alterations in the vasa vasorum, the histologic specimens in cases of dissecting aneurysm of the aorta.

MATERIAL AND METHODS

Fourteen consecutive instances of dissecting aneurysm of the aorta, taken from the autopsy protocols of Michael Reese hospital for the years 1930 to 1947, inclusive, were reviewed from the clinical and morphologic point of view, 11 with emphasis on changes in the vasa vasorum. Whenever possible, numerous blocks of tissue were examined. These were taken from the relatively uninvolved zones of the aortas, as well as from the sites of rupture or perforation. Sections were routinely stained with Delafield's hematoxylin and eosin and, whenever feasible, with orcein and with Masson's trichrome stain.

CLINICAL FINDINGS

Age and Sex.—There were 3 females and 11 males in the group; their ages ranged from 26 to 70 years, the average being 53. Three were under 40.

Hypertension.—In only 1 instance was there a definite history of long-standing hypertension. After the onset of dissection, the systolic and diastolic blood pressures were elevated above the normal range in 4 cases. The systolic pressure only was elevated in 2 additional cases and the diastolic pressure only in 2 others. In the case of 1 patient, with a healed old dissection, the blood pressure was normal throughout the course in the hospital. In another case, in which the patient had aortic regurgitation, the blood pressure was 140 systolic and 35 diastolic before dissection and 150 systolic and 60 diastolic after dissection. Multiple small renal hemorrhages were observed in the latter instance at the postmortem examination.

Onset.—We obtained information about the onset of the condition in 11 cases. Pain was present in each, and it was the most conspicuous feature in all but 1. In 9, it was severe and sharp from its inception. One patient had pain in the chest, slight at first, which progressively increased; the site of the pain varied,

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7. Hueper, W. C., and Ichniowski, C. T.: Experimental Studies in Cardiovascular Pathology: Late Vascular Reactions of Histamine Shock in Dogs, Am. J. Path. **20**:211-221, 1944; Hematic and Organic Reactions in Standardized and Graded Histamine Shock in Dogs, J. Pharmacol. & Exper. Therap. **78**:127-138, 1943.

and there was a tendency for it to shift from one area to another. The location of the pain, in most instances, could be correlated with the extent of the dissection. In 2 cases in which pain had been localized to the thorax, the dissection was found to involve most of the abdominal aorta.

Physical Findings.—These data were available for 12 patients, the other 2 having died before admission to the hospital. Cardiac murmurs of assorted types, were present in 6 cases. Aortic diastolic murmurs were present in 3 cases, in 1 of which the patient had a previous old aortic insufficiency. Two patients showed physical signs of pleural effusion. In 4 cases in which the patients showed evidence of abdominal tenderness, spasm and rigidity, the dissection was found to involve the abdominal aorta. One patient [8] had a large ecchymosis in the left lower quadrant of the abdomen, and 2 had loss of circulation in a limb.

Laboratory and Roentgenographic Findings.—The white blood cell count, when available, was elevated, ranging from 10,200 to 29,900 cells per cubic millimeter. One patient, in whom the dissection involved the renal artery, had gross hematuria. Roentgenograms taken of the thorax of 3 of 5 patients showed evidence of increased aortic shadows.

Electrocardiographic Findings.—Electrocardiograms were taken during the acute episode in 8 cases, with serial records in 3. In 1 instance, the record was within normal limits. Four patients showed strain of the left side of the heart; 1 patient's heart was considered abnormal, with nonspecific changes. Single records of 2 patients were considered to be indicative of possible recent myocardial infarction.

The electrocardiographic pattern of acute pericardial tamponade due to a hemopericardium was seen to develop in the case of 1 patient with strain of the left side of the heart.

It has been stated generally that the chief value of the electrocardiogram is in distinguishing dissecting aneurysm from recent myocardial infarction. However, Weiss,[9] Wainwright [10] and Baer and Goldberg [11] have all reported cases in which the dissection extended into the coronary artery, with resultant occlusion of the vessel and a myocardial infarction. In the present study, the electrocardiograms showed the expected evolution of recent myocardial infarctions.

Duration and Course.—The duration varied. Two of our patients had old dissecting aneurysms. One of these was healed, but there was nothing suggesting its age. The other patient had had an acute episode, for which he had been hospitalized elsewhere ten months previously. At that time sudden thoracic pain developed and he lost consciousness for several hours. There was transient paralysis of the left leg and loss of pulsations in the left carotid artery and the brachial arteries, despite which the patient was able to return to work.

In the fatal cases of shortest duration, there was steady progression, usually without relief from pain, until death ensued. With 1 exception patients surviving immediate effects had gradual easing of the pain and other symptoms, but several had periodic exacerbations. After varying intervals, death occurred suddenly.

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8. Green, R., and Saphir, O.: Ecchymoses of the Abdominal Wall as an Early Diagnostic Sign of Dissecting Aneurysm of the Aorta, to be published.

9. Weiss, S.: Dissecting Aneurysm of the Aorta: Two Cases with Unusual Features, New England J. Med. **218**:512-517, 1938.

10. Wainwright, C. W.: Dissecting Aneurysm Producing Coronary Occlusion by Dissection of Coronary Artery, Bull. Johns Hopkins Hosp. **75**:81-94, 1944.

11. Baer, S., and Goldberg, H. L.: The Varied Clinical Syndromes Produced by Dissecting Aneurysm, Am. Heart J. **35**:198-211, 1948.

Prognosis.—It has been stated that about 10 per cent of dissecting aneurysms will heal.[12] Two of our patients survived the initial episode, 1 dying of a recurrence and the other of congestive heart failure. One of us (J. G. S.)[13] previously reported a case in which the patient was alive four years after the acute episode.

ANATOMIC OBSERVATIONS

Heart.—Hypertrophy involving primarily the left ventricle of the heart was present in almost every instance. The average weight of the hearts was 565 Gm.

Pronounced coronary sclerosis was present in most instances; in addition, 1 heart showed an old myocardial infarction. The dissecting aneurysm had ruptured into the pericardial cavity in 6 instances.

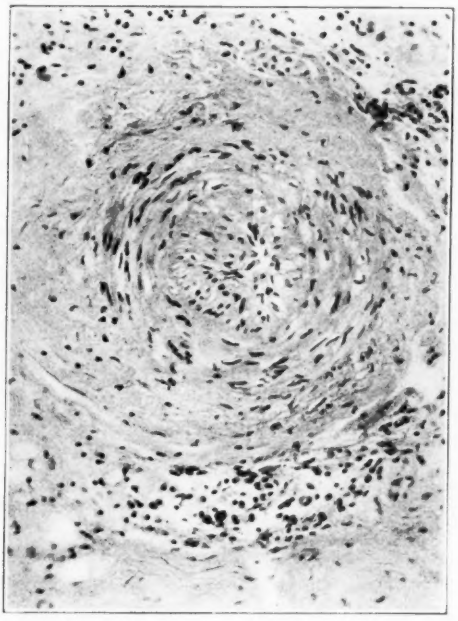

Fig. 1.—Small artery of the vasa vasorum, with pronounced muscular hyperplasia and intimal proliferation resulting in an extremely narrowed lumen. Note small accumulations of lymphocytes in the adventitia. × 160; iron hematoxylin and eosin stain.

Aorta.—Dissecting aneurysms were present in 14 instances. Medionecrosis fulfilling Erdheim and Gsell's criteria was present in 12. Two patients had extreme arteriosclerosis of the entire aorta, with many atheromatous ulcers.

12. Weiss, S.; Kinney, T. D., and Maher, M. A.: Dissecting Aneurysm of the Aorta with Experimental Atherosclerosis, Am. J. M. Sc. **200**:192-203, 1940.

13. Schlichter, J. G.: Beitrag zu den Aneurysmen und Rupturen des Herzens. Lausanne, Switzerland, Imprimerie Held, 1940.

Dissection in these cases could be traced to undermining of the intima and the media beneath arteriosclerotic plaques; it was localized to the abdominal aorta in 1 and diffuse in the other. Alterations of the vasa vasorum were minimal in both cases, with no medionecrosis. In contrast, 2 other aortas, with moderate to pronounced atheromatosis and arteriosclerosis and with typical medionecrosis, showed profound narrowing of the vasa vasorum. Both of the latter had muscular and intimal hyperplasia of the vasa vasorum; in 1 there was also narrowing by atheromatous plaques and splitting of the intima and the internal elastic membranes of the adventitial vessels. Diffuse atheromatosis, but no arteriosclerosis, was present in another aorta with medionecrosis.

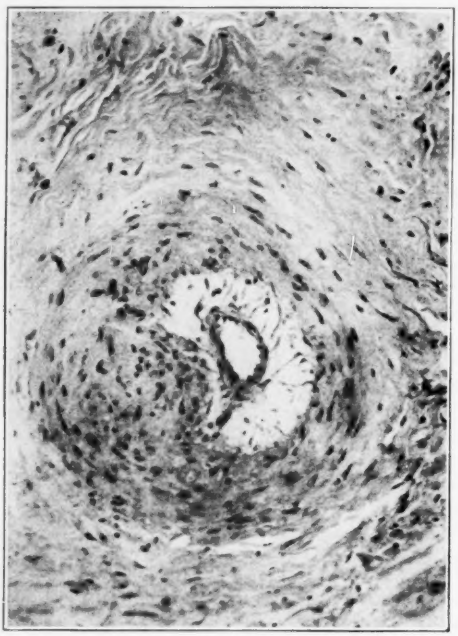

Fig. 2.—Small artery of the vasa vasorum, illustrating pronounced luminal narrowing resulting from subintimal deposition of lipids. ×160; iron hematoxylin and eosin stain.

Two aortas with narrowings of the vasa vasorum suggested the possibility of rheumatic arteritis because of typical associated endocardial changes and because of perivascular infiltrations of the vasa vasorum.

Changes in the Vasa Vasorum.—The histologic changes encountered in the cases of medionecrosis have previously been described in detail.[14] The vasa vasorum of 9 aortas showed narrowing of the lumens of varying types and

14. Amromin, G. D.; Schlichter, J. G., and Solway, A. J. L.: Medionecrosis of the Aorta, Arch Path. **46**:380-385 (Oct.) 1948.

Fig. 3.—Roentgenogram of the vasa vasorum of the root and arch of the aorta in a patient with a dissecting aneurysm. Note lack of filling of the vasa vasorum a short distance above the cusps. This zone corresponded with the site of rupture of the dissecting aneurysm and with the most severe alterations in the vasa vasorum.

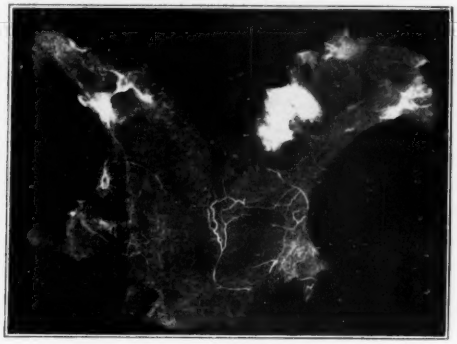

Fig. 4.—Roentgenogram of the vasa vasorum at the root of a normal human aorta injected with radiopaque material. The aortic cusps are at the bottom of the illustration.

severity. Changes were outstanding in those aortas showing medionecrosis. Alterations consisted of hyperplasia of the media (fig. 1) and of splitting and reduplication of the internal elastic membrane with or without subintimal deposition of lipids (fig. 2). In addition to varying combinations of these changes, the smallest vessels presented hyperplasia or swelling of endothelial cells and a collagenous type of degeneration without inflammatory reaction.

The abnormalities in the vascularity of 1 aorta were demonstrated by injection of its vasa vasorum with radiopaque material; a roentgenogram of the aorta was then made (fig. 3). This procedure had previously been followed by one of us (J. G S.) in the study of aortas removed from dogs [15] as well as of normal human aortas [16] (fig. 4). Lack of filling of vessels near the site of rupture was seen to be associated with severe medial and intimal changes. This method of demonstrating abnormalities of the vasa vasorum might well be used more frequently in instances of dissecting aneurysms and isthmic stenoses of the aorta.

COMMENT

Since the original articles by Gsell and Erdheim describing medionecrosis of the aorta, there has been an increasing amount of morphologic and experimental evidence to suggest that the lesion is essentially the result of local ischemia. Medionecrosis of the aorta or the peripheral vessels has been produced experimentally by chemical or mechanical interference with the vascularization, as carried out through the vasa vasorum in the adventitia.[5] Recently it was demonstrated that, through interference with the vascularization of the ascending aortas of dogs, it was possible to produce medionecrosis and its sequelae, dissecting aneurysm, spontaneous rupture or saccular aneurysm.[5]

Comparing the medionecrotic lesions produced in various species of animals by a wide variety of methods with the lesion in man, one may conclude that the vascularization of the aorta determines their site, extent and severity.[17] Differences in the susceptibility to ischemia of the aortic wall in different species are due to variations in the vascularity of the aorta. That of the rabbit is the poorest, that of the dog the richest and that of man somewhere between. The excellence of the aortic vascularization of the dog may explain the difficulty encountered in attempting experimental production of medionecrosis in that animal, and the ease of experimental production of medionecrosis in the rabbit may be due to its poor vascularity.[17]

It may be concluded, therefore, that anoxia of the vascular wall is apparently the most important factor in the development of medionecrosis. Such anoxia may develop as a result of various factors:

15. Schlichter, J. G.: Studies on the Vascularization of the Aorta: I. The Vascularization of the Aorta in the Normal Dog, Am. Heart J. **32**:770-777, 1946.

16. Schlichter, J. G.: Vascularization of the Aorta in Different Species in Health and Disease, Am. Heart J. **35**:850-851, 1948.

17. Schlichter.[5] Schlichter. [15]

1. Obstructive or occlusive diseases of the vasa vasorum. Such conditions are demonstrable morphologically; they had been noted previously in 9 of our cases. There was usually arteriolosclerosis, arteriosclerosis or other alterations of the hyperplastic variety.

2. Alterations in the hemodynamics of the vasa vasorum. Dilatation with resultant stasis of blood may explain dissecting aneurysms first becoming manifest after shock or severe infections in man. Medionecrosis experimentally produced in rabbits by injection of epinephrine (adrenalin®) may be secondary to vasoconstriction of the adventitial vessels.

3. Diminished oxygen saturation of the blood or severe anemia. This factor alone rarely, if ever, results in medionecrosis; however, when combined with other mechanisms it may play an important role.

4. Congenital abnormalities in the distribution of the vasa vasorum or paucity of collateral circulation through the adventitia or the outer third of the media. Poor vasculature may be an important cause; it can be demonstrated adequately only by injection of the vasa vasorum with radiopaque material. The high frequency of dissecting aneurysm in cases of isthmic stenosis may be secondary to this factor.

5. Any combination of these factors.

Hypertension is important in several respects. It is considered the cause of hyperplastic intimal changes of small arteries, which may include the vasa vasorum. Such changes in the vasa vasorum may be the immediate or contributory cause of medionecrosis. As a result of ischemia of portions of the aorta, the media undergoes infarction or necrosis. The disorder may manifest itself in zones showing loss of structure or in accumulations of loose connective tissue. Progression of the lesion may result in evidence of healing, as described by Erdheim.[2] After the medionecrosis is established, even in normotensive persons, transitory hypertension, such as that produced by physical or emotional stress, may increase the spread of the dissection as well as increase its chance of rupture.

The concept of zones of ischemia of the aorta has been suggested by some authors who state the belief that dissecting aneurysms may result from rupture of the vasa vasorum. Such a mechanism, i. e., vasospasm with necrosis of the distal portion of the vessel, could probably play a role in some cases of hypertension without histologic alterations being apparent in the vasa vasorum.

The limitation or the severity of the dissection is often determined by previous pathologic changes in the aorta. A vessel scarred from long-standing syphilis will rarely permit extensive spread of the dissection, presumably because of the many firm old scars. Likewise, severe sclerosis of the aorta, with many large arteriosclerotic plaques

involving the intima as well as impinging on the inner portion of the media, tends to limit the spread of the dissection. A relatively normal aorta which is subjected to medionecrosis by anatomic or physiologic ischemia manifest through the vasa vasorum will usually show the most extensive dissections.

Healing of medionecrotic lesions depends to a large extent on the adequacy of collateral circulation.[5] Even arteriosclerotic ulcers which undermine and tend to form localized or diffuse medial dissections may be limited in their spread, not only by previous scarring of the media, but also by a tendency to heal through thrombosis and scarring. The latter may be greatly facilitated when there is adequate collateral circulation through the vasa vasorum. In cases of dissection following undermining of arteriosclerotic plaques, as well as in those few cases of dissection without intimal rupture, the separation of the aortic wall from its proper blood supply may be responsible for the formation and spread of dissecting aneurysms.

The most frequent demonstrable pathologic alterations found in aortas with dissecting aneurysms are medionecrosis, undermined arteriosclerotic ulcers and, rarely, syphilitic lesions. The first is by far the commonest.

We encountered pathologic changes in the vasa vasorum in 9 of our cases of dissecting aneurysm. The changes varied from slight to pronounced arteriolosclerosis and arteriosclerosis, with hypertrophy or hyperplasia of the media and the intima. In all 9 cases, luminal narrowings were present. Abnormalities in the distribution and filling of the vascular bed were demonstrated at autopsy in the 1 aorta in which injection of the vasa vasorum with a radiopaque material was carried out.

Since some of our 14 patients were hypertensive, a recent study of the aortas of 40 patients with hypertension[18] is of interest. Twenty-three of these aortas showed changes in the adventitia, with frequent accumulations of lymphocytes. In 35 per cent, however, there were hypertrophy of the media of the vasa vasorum and occasional luminal narrowing caused by subendothelial deposition of hyalin. For the most part, these findings are in accord with ours.

We examined the ascending aortas of 20 normotensive patients whose ages averaged 51.3 years. Medial hyalinization of the vasa vasorum without luminal narrowings was encountered in the cases of 5 patients, of whom 2 were 61 and 1 each 66, 72 and 76. In the aortas of 4 other patients, aged 22, 50, 66 and 73, respectively, narrowings of the lumens of the vasa vasorum were observed in addition to medial or

18. Ashworth, C. T., and Haynes, D. M.: Lesions in Elastic Arteries Associated with Hypertension, Am. J. Path. **24**:195-205, 1948.

intimal hyperplasia. Interestingly enough, the patient aged 22 exhibited early disruption of the outer third of the media of the aorta, resembling medionecrosis near the zones of alteration in the vasa vasorum. Luminal narrowings of a group of small arteries of the vasa vasorum in the patient aged 73 were at the immediate site of an extremely large arteriosclerotic plaque which impinged on and disrupted the inner third of the media of the aorta. Excluding these 2 persons, only 2 of the 20 routine controls had alterations of the vasa vasorum without medial or pronounced intimal changes in the aorta. These alterations were less pronounced and less extensive in comparison with those of the group with dissecting aneurysms.

Two of the dissecting aneurysms occurred in aortas with isthmic stenosis. The ages of the patients were 26 and 29, respectively. The hearts weighed 530 Gm. and 400 Gm. Changes were found in the vasa vasorum of only 1 of these.

Still to be explained is the great predilection of dissecting aneurysms, particularly those which rupture, for the ascending aorta. Variability in vascularization of the ascending aorta is much greater than that of the descending aorta. Rottino [4d] has shown medionecrosis of the variety usually encountered in the ascending portion to be present also in the arch and in the descending aorta. How can this be reconciled with the much greater incidence of dissection at the root? Other differences are immediately evident. The ascending aorta is much more mobile and bears the greater direct brunt of the blood stream as it leaves the heart. The ascending aorta and the arch are not surrounded and protected by connective tissue and neighboring organs, as is the descending aorta. Also, the frequent ostiums arising from the aorta beyond the arch in all probability provide sufficient nourishment to the aorta directly from the lumen to compensate for any alterations or depletions in the adventitial blood supply.[5]

Reviewing our own cases and the voluminous literature on dissecting aneurysm of the aorta, it becomes apparent that this disease has not one but several backgrounds, depending on varying physiologic and morphologic alterations in the wall of the aorta. The pathologic picture itself will vary with the etiologic factor. All cases, however, have one feature in common—the destruction of the aortic media. In an aorta so damaged, normal or increased intra-aortic pressure may cause spontaneous rupture or the formation of a dissecting aneurysm and rupture.

Since destruction of the aortic media is the common feature of dissecting aneurysm, it may be suggested on the basis of evidence that the factor responsible for this idiopathic cystic necrosis of the aorta is ischemia of its media. This condition can be brought about by pathologic changes in the vasa vasorum, resulting in narrowing of their lumens. Such alterations in the vasa may be due to a localized variety

of arteriolosclerosis or arteriosclerosis and may or may not be associated with similar changes elsewhere, particularly in the kidneys.

SUMMARY

The morpohologic and clinical aspects of 14 cases of dissecting aneurysm of the aorta are reviewed. Two of these were due to arteriosclerosis; 12 were secondary to medionecrosis of the aorta.

Alterations were encountered in the vasa vasorum of 9 aortas; seven of the 9 showed associated medionecrosis of the aorta.

CONCLUSION

Ischemia of the media of the aorta was implicated as the underlying primary factor in the production of medionecrosis. Various experimental, physiologic, anatomic and congenital factors may, singly or in combination, bring about medionecrosis and dissecting aneurysm.

HEMATOLOGIC STUDIES IN HIROSHIMA AND A CONTROL CITY TWO YEARS AFTER THE ATOMIC BOMBING

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Control Studies on Americans
Statistical Procedures
Presentation of Data
Over-All Blood Picture
Relation Between Age and Sex and Response to Atomic Bombing
Relation Between Traumatic Injuries and Flash Burns and Hematologic Observations
Relation Between Amount of Radiation and Hematologic Observations
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Summary

INTRODUCTION

THE ATOMIC bomb explosions in Hiroshima and Nagasaki, in August 1945, subjected large numbers of persons to significant amounts of radiation. The immediate, acute effects of the exposure have been evaluated by a group of United States Army and Navy and Japanese civilian investigators, usually referred to as the Joint Commission.[1] Their observations did much to confirm and extend the already recognized picture of acute radiation sickness and the early periods of recovery in man. There exists, then, at the present time, a considerable body of knowledge pertaining to the findings during the first few months after the exposure of man to ionizing radiation.

In contrast, relatively little is known concerning the late effects of irradiation of the whole body in man, such as may develop after apparent recovery. The data which do exist deal largely with the sequelae of repeated exposure to small doses occurring in radiologists before the necessity of adequate shielding was fully recognized, or following chronic poisoning with long-lived radioactive elements. A large number of the survivors of Hiroshima and Nagasaki, on the other hand, were persons who had received in an extremely brief time varying amounts of ionizing radiation, ranging from negligible to the maximum tolerable. The need for long range, detailed, methodical studies of the cases of these persons cannot be overstated in an era when increasing numbers of people will, in the very nature of current scientific developments, be exposed to significant amounts of radiation. Recognition of this fact resulted in the issuance, on Nov 26, 1946, of a presidential directive, charging the National Research Council with the responsibility of conducting appropriate studies of the surviviors of Hiroshima and Nagasaki. The background for this directive, as well as for subsequent organizational developments, has been briefly detailed elsewhere.[2]

1. Report of the Joint Commission, to be published.

2. Genetic Effects of the Atomic Bombs in Hiroshima and Nagasaki, Genetics Conference, Committee on Atomic Casualties, National Research Council, Science **106**:331 (Oct. 10) 1947.

One of the foremost of the many problems clamoring for investigation relates to the cellular elements of the blood. The studies described in the present paper were carried out in Hiroshima and Kure, Japan, from March 1947 to April 1948. They were designed to answer the question: What is the peripheral hematologic picture twenty to thirty-three months after atomic bombing in persons who received large amounts of radiation to the whole body? Such studies serve the dual purpose of attempting to evaluate the current hematologic status of these persons and of providing a base line by comparison with which subsequent developments may be appreciated.

PRESENT DAY CONDITIONS IN JAPAN

A reference to health conditions in Japan at the time of this report is essential to an understanding of some of the problems and difficulties which beset a survey study of the present type. Japan suffered rather severely during the previous decade. The maintenance of a large fighting force necessarily invoked considerable privation on the general populace. Japan had never been a country of abundance and, in fact, was existing at a near equilibrium level during the prewar days. The increased demands imposed by the war reduced the general standard of living significantly beneath the initial plane. The lowest ebb of general conditions was probably reached shortly after the cessation of hostilities. During the several years previous to this report there has been a considerable improvement in living standards, but at the time of writing many essential commodities remain in short supply. Available provisions consist, for the most part, of the carbohydrate staple products, seasonal vegetables and a small amount of fish. Only on festive occasions does the average family enjoy significant amounts of animal fat and protein. The official government ration during the period covered by these studies was about 1,500 calories a day. Inflation had forced the cost of the necessary additional calories to fantastic levels.

Although a full appreciation of the true circumstances and conditions is difficult without firsthand observations, it may be appreciated that the general health conditions parallel the standard of living. This is well illustrated by the reported tuberculosis mortality rates for four years[3]: In 1944, there were 240.2 deaths per 100,000 persons; in 1945, 280.0; in 1946, 264.2, and in 1947, 189.0. For comparison, the mortality rate in the United States in 1945 for all forms of tuberculosis

3. Phelps, L. V., Chief, Division of Vital Statistics, Public Health and Welfare Section, General Headquarters, Supreme Commander for the Allied Powers: Personal communication to the authors.

was 40.1 deaths per 100,000 persons.[4] Imamura,[5] in a recent photofluorographic survey of 144,350 persons in Osaka and its suburbs, observed 2.0 per cent with active tuberculosis and 1.5 per cent with suspected lesions. The morbidities of ascariasis and ancylostomiasis among the general population have been estimated to be from 80 to 90 per cent and from 50 to 60 per cent, respectively.[6] Dysentery and diarrhea, due to a variety of causes, are much more prevalent than in the United States.

Thus, despite the significant accomplishments of the Public Health and Welfare Section, General Headquarters, Supreme Commander for the Allied Powers,[7] and the strenuous postwar efforts of various Japanese groups, health conditions in Japan during the period covered by this study were significantly below those in the United States, a fact extremely pertinent to any consideration of the results described.

PLAN OF OBSERVATION

General Data.—An attempt was made to compare certain aspects of the hematologic status of Japanese of Hiroshima who, at the time of the atomic bombing, had been relatively heavily irradiated with the findings for an appropriate control group. The minimum interval in man between exposure to radiation and development of such possible late hematologic complications as leukemia or aplastic anemia is known only vaguely. The rapidity and degree of completeness of hematologic recovery in a group such as that irradiated in Hiroshima is unknown. Adequate follow-up studies in Hiroshima, therefore, called for frequent sampling of the irradiated population. Unfortunately, between the termination of activities of the Joint Commission [1] and the initiation of the investigations of the Atomic Bomb Casualty Commission there elapsed, for various reasons, a period of some sixteen months, during which only a few observations were made; these were largely by

4. Natality and Mortality Data for the United States Tabulated by Place of Residence, in Vital Statistics of the United States 1943, United States Department of Commerce and Labor, Bureau of the Census, 1945, pt. 2.

5. Imamura, A.: The Epidemiology and Prevention of Tuberculosis in Japan, read before the Eleventh Meeting of the Japanese Medical Association, 1947.

6. Duff, F. L.: Personal communication to the authors.

7. A Review Covering a Résumé of the Problems, Accomplishments, and Future Programs of the Public Health and Welfare Section Among the Japanese Population in Furthering the Objectives of the Supreme Commander, for the Period August 1945-August 1947, General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, 1947.

Japanese groups working under considerable handicap. Moreover, the early activities of the Atomic Bomb Casualty Commission were largely exploratory and not designed to support a large scale study. Hiroshima, in 1947, contained very little in the way of laboratory facilities, and the city was depleted of much of its native medical and technical talent. The plan whereby our observations were carried out represents a compromise between inadequate laboratory and technical facilities and the desirability of getting observations under way as quickly as possible.

Subjects.—The survivors of the Hiroshima bombing received varying amounts of radiation, according to their distance from the explosion and the amount of shielding protecting them. In this first survey it was felt desirable to study those persons who had received relatively large doses of radiation. The Joint Commission had established the fact that epilation of the scalp was one of the more reliable and objective signs of the absorption of large amounts of radiation.[1] It may be assumed that the majority of persons who received sufficient radiation to the scalp to cause epilation received corresponding amounts of radiation to the whole body. The epilating dose of gamma radiation of this type is estimated to be about 400 r. Consequently, epilation was utilized as the criterion for the selection of subjects. In order to control the observations on these irradiated persons, parallel studies on comparable nonirradiated persons were carried out in the city of Kure. Located 18 miles (28.97 kilometers) from Hiroshima, and about half its size, Kure is also a seaport town, with a comparable population pattern and nutritional status.[8] Being the site of a principal naval base, it had been subjected to severe incendiary and explosive bombing raids, with extensive damage, although casualties were extremely few in comparison with Hiroshima.

Precautions.—Prerequisite to a study of this type are the elimination of as many undesirable varieties as possible and the observation of sufficiently large samples to validate the results statistically. Sampling was executed in such a manner as to insure maximum comparability of the two groups, aside from the factor of radiation. For instance, it was well appreciated that a large number of the survivors of Hiroshima, pretentiously suffering from "atomic bomb disease," would desire inclusion in such an investigation, with the hope of receiving treatment and advice for their ailments, the symptoms of which most conveniently dated from the atomic bombing. The inclusion of such

8. Howe, F. A.: Public Health and Welfare Section, General Headquaters, Supreme Commander for the Allied Powers: Personal communication to the authors.

persons in a sample would obviously have created a bias in the form of extraneous pathologic factors, which would have been extremely difficult to duplicate in parallel controls.

In order to minimize the occurrence of unrelated hematologic complications and biologic variation, as well as for reasons of convenience, it was felt desirable to study, so far as possible, the younger age groups in schools.

To eliminate such systematic errors as might have arisen through the use of different groups of technicians in the two laboratories, all observations in the two cities were made by the same technicians, who alternated days between Kure and Hiroshima. During the last four months of the investigation, as many as possible of the originally selected subjects were reexamined and the results of the two observations averaged, thereby reducing seasonal changes and possible systematic laboratory errors. Actually, only about one half of the subjects were reexamined, the interval between the two examinations varying from three to eight months.

Finally, to test the comparability of our technics and results with those of other investigators, a small group of 25 United States Army personnel were examined.[9]

GENERAL PROCEDURES

A random selection of epilated subjects, with the elimination of a maximum of undesirable bias of the aforementioned type, was insured through the adoption of a screening questionnaire. This included a variety of direct questions, relating to the subject's injuries and to his symptoms after the atomic bombing. The form was distributed to many of the schools in Hiroshima and likewise to a randomly selected portion of the remainder of the civil population. Approximately 16,000 screening questionnaires were completed. Those persons listing epilation were requested to report for examination. All were unaware of the criterion of selection.

In Kure, selection of the control sample was achieved through the principals of the various schools and through various local organizations, persons being selected to equate in sex and age to those actually examined in Hiroshima. All heads of organizations responsible for selection were fully appreciative of the possibility of undesirable bias arising from the inclusion of "volunteers." The accompanying histogram indicates comparison, by age and sex, of the epilated and control samples.

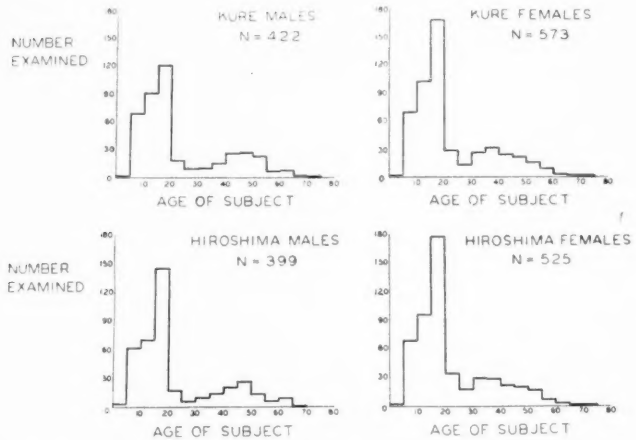
The selected subjects, on reporting to the laboratory for examination, were interviewed by a trained interpreter, who, after asking specific, direct questions, completed a detailed questionnaire. The items on the record were chosen in an attempt to bring out possible significant relations between hematologic findings and the history at the time of the bombing, with emphasis on position of the subject

9. The United States Army personnel were volunteers from the Chugoka Military Government Region and the Hiroshima Military Government Team, whose headquarters were in Kure.

at the time of the explosion, signs and symptoms of radiation sickness, and associated trauma. It should not be assumed that the record in all instances represents an entirely true account, considering the fact that the interview was conducted eighteen to thirty months after an intense experience.

A similar questionnaire was used for the controls, but in the section devoted to the history only identifying information was recorded.

After the interview, a brief physical examination was carried out, with particular regard to general health, extent of injuries and occurrence of gross pathologic features. Persons with minor infections were common and were not eliminated from the series. Comparable examinations were made on both epilated and control groups. No physical examination was made at the time of reevaluation.



Frequency distribution of the population samples according to sex and age

An attempt was made to secure the following hematologic data for each subject: erythrocyte, leukocyte and differential counts; hemoglobin concentration; hematocrit reading, and plasma protein values. In addition, reticulocyte counts were obtained for a limited number of persons. Leukocyte and differential counts were made on blood flowing freely from an incision of the ear lobe. The remaining observations were made from a 5 cc. sample of venous blood, drawn with no particular reference to meal time; all precautions were taken to avoid stasis. However, it should be noted that during the cold months, with the absence of adequate heating and, in some instances, adequate clothing, the peripheral circulation of the extremities was in many persons relatively static, as evidenced by slight cyanosis of the fingers. This factor introduced the possibility of some seasonal variation but did not invalidate the results, for the climatic conditions were comparable in the two laboratories. The venous sample was placed in a clean, dry tube containing 5 mg. of potassium and ammonium oxalate, in the proportions

recommended by Heller and Paul.[10] The various hematologic determinations were usually made within an hour, and always within four hours, of the time the specimen was secured.

HEMATOLOGIC PROCEDURES AND EVALUATION OF ERRORS

Erythrocyte and Leukocyte Counts.—The erythrocyte count was carried out in the standard manner, using Army-Navy equipment which was not certified by the United States Bureau of Standards. Dilutions of 1:200 were made with filtered Hayem's solution, samples of blood being withdrawn from the well mixed oxalated venous sample. Pipets were vigorously shaken for three to five minutes just prior to filling the chamber. Counting was carried out in 5 0.004 cu. mm. volumes. Duplicate dilutions and counts were made in all instances. When the original pair differed by more than 400,000 cells per cubic millimeter, one or more additional dilutions and counts were made. The average of all counts was taken as the final value. (The practice of utilizing only that pair of a series of repeated counts on the blood of an individual subject which differs no more than a set amount is statistically an unsound procedure. The establishment of a range limit, by which a pair of counts may acceptably differ, should be considered only as a means to aid in the detection of technical errors.)

Leukocyte counts were also carried out in the customary manner. Capillary blood was routinely employed; dilutions of 1:20 were made with filtered Turk's solution.[10a] Pipets were vigorously shaken for three to five minutes just prior to filling the counting chamber. Counting was carried out in 4 0.1 cu. mm. volumes. Duplicate dilutions and counts were made in all cases. When the difference between the pair of counts was greater than 20 per cent of the mean, additional dilutions and counts were made if the subject was still available; otherwise, the original pipets were reshaken and the leukocytes recounted. In every case, the final value accepted was the average of all counts.

The problem of error involved in the estimation of numbers of erythrocytes and leukocytes has been examined by several investigators.[11] The work of Berkson and his collaborators [11 e-g] was most extensive. They carried out repeated dilutions and counts on a series of blood samples, utilizing standard pipets and a photographic-mechanical method of enumerating blood cells in a standard chamber.

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10. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. & Clin. Med. **19**:777 (April) 1934.

10a. The composition of Turk's solution is described in Stitt, E. R.; Clough, P. W., and Clough, M. C.: Practical Bacteriology, Haematology and Animal Parasitology, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1938, p. 299.

11. (*a*) "Student": On the Error of Counting with a Haemacytometer, Biometrika **5**:351 (Feb.) 1907. (*b*) Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte: Methods of Determination and Clinical Application, J. Lab. & Clin. Med. **17**:899 (June) 1932. (*c*) Ponder, E.; Saslow, G., and Schweizer, M.: On Variations in the White-Cell Count of Man, Quart. J. Exper. Physiol. **21**:21 (April) 1931. (*d*) Bryan, W. R.; Chastain, L. L., and Garrey, W. E.: Errors of Routine Analysis in the Counting of Leukocytes, Am. J. Physiol. **113**:416 (Oct.) 1935. (*e*) Magath, T. B.; Berkson, J., and Hurn, M.: The Error of Determination of the Erythrocyte Count, Am. J. Clin. Path. **6**:568 (Nov.) 1936. (*f*) Berkson, J.; Magath, T. B., and Hurn, M.: Error of Estimate of Blood Cell Count as Made with Hemocytometer, Am. J. Physiol. **128**:309 (Jan.) 1940. (*g*) Berkson, J.: Blood Cell Count: Error; in Glasser, O.: Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, p. 110.

In these circumstances, the standard deviation for the determinations on any one sample was ± 390,000 cells when the mean was approximately 5,000,000 cells per cubic millimeter, resulting in a coefficient of variation of (0.390/5.00) × 100, or 7.8 per cent. When each item in the frequency distribution of counts was an average of duplicate dilutions and counts, the standard deviation was reduced to $\frac{1}{\sqrt{2}} \times 0.390$, or ± 276,000 cells, and the coefficient of variation for the paired count means was 5.5 per cent. Approximately 95 per cent of the averages of all duplicate counts on a single blood sample might be expected to fall within ± 552,000 cells (twice the standard deviation), or ± 11.0 per cent of the mean, at a mean of 5,000,000 cells.

Similarly, in regard to enumeration of leukocytes by the standard procedure, the coefficient of variation of a distribution of repeated dilutions and counts on a single sample of blood containing about 7,000 leukocytes per cubic millimeter was 10.7 per cent. The use of the averages of duplicated dilutions and counts reduced this to $\frac{1}{\sqrt{2}} \times 10.7$ per cent, or 7.6 per cent; approximately 95 per cent of paired count means might then be expected to fall within ± 15.2 per cent of the mean, if the mean were approximately 7,000 leukocytes per cubic millimeter.

The errors in these two hematologic procedures are considerably greater than is generally appreciated.

Determination of Hemoglobin and Plasma Protein Content.—These determinations were made by the copper sulfate method for measuring specific gravity, as described by Phillips and others.[12] One hundred cubic centimeter portions of copper sulfate solutions, graded at intervals of 0.001 Gm. per cubic centimeter, were prepared according to instructions with appropriate dilutions of a stock solution, prepared either from commercially weighed samples of copper sulfate or by the saturation technic. Each set so prepared was calibrated by direct measurement of the specific gravity of representative samples, either with a calibrated hydrometer or by comparing the weight of a filled pyknometer with that of one filled with water at the same temperature. During the last six months of the survey, the solutions were prepared in 200 cc. portions and divided into two sets, one for the Kure laboratory and the other for the Hiroshima laboratory. Venous blood was used for all determinations and correction applied for the anticoagulant. Each set was used for determinations on the blood of not more than 100 persons. The bulk of the data represent single determinations, but occasionally an average of two determinations made by different independent technicians was employed. The revised nomogram was utilized to compute the hemoglobin concentration and the protein values.

The usefulness and relative accuracy of the determination of specific gravity of whole blood and plasma, in estimating the hemoglobin concentration and plasma protein content of blood, which is not grossly abnormal, have been well estab-

12. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K.; Hamilton, P. B., and Archibald, R. M.: Copper Sulfate Method for Measuring Specific Gravity of Whole Blood and Plasma, New York, Josiah Macy, Jr. Foundation, 1945.

lished,[13] although two investigators[14] have failed to demonstrate satisfactory correlation between the specific gravity of the plasma or serum and its protein content. The propriety of using this method in determinations on grossly abnormal blood is still open to question.

In an attempt to evaluate at least a portion of the error of this method in our laboratories, duplicate estimates of hemoglobin content were made by two independent technicians in 191 cases. Statistical analysis of the differences revealed no significant systematic error on the part of either technician; that is, regarding the mathematical sign of the differences, the mean difference was -0.01 ± 0.016 Gm. per cubic centimeter.[15] The standard deviation of the distribution of the differences was ± 0.22 Gm. per cubic centimeter. Taking twice the standard deviation as indicating the significant limits of variability, 95 per cent of the absolute differences between duplicate estimations were within 0.44 Gm. per hundred cubic centimeters. Utilizing the fact that the standard deviation of differences is equal to $\sqrt{2}$ times the standard deviation about the mean, one can estimate from the variation of

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13. (*a*) Phillips and others.[12] Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, J. Biol. Chem. **69**:625 (Aug.) 1926. (*b*) Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis, J. Clin. Investigation **8**:337 (April) 1930. (*c*) Weech, A. A.; Snelling, C. E., and Goettsch, E.: The Relationship Between Plasma Protein Content, Plasma Specific Gravity, and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis, ibid. **12**:193 (Jan.) 1933. (*d*) Nugent, R. L., and Towle, L. W.: The Specific Gravity of Synthetic Solutions of Serum Albumin and Serum Globulin, J. Biol. Chem. **104**:395 (Feb.) 1934. (*e*) Weech, A. A.; Reeves, E. B., and Goettsch, E.: The Relationship Between Specific Gravity and Protein Content in Plasma, Serum, and Transudate from Dogs, ibid. **113**:167 (Feb.) 1936. (*f*) Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: II. The Estimation of Total Protein Content of Human Plasma and Serum by the Use of the Falling Drop Method, J. Clin. Investigation **17**:373 (July) 1938. (*g*) Ashworth, C. T., and Adams, G.: Blood Specific Gravity Studies, J. Lab. & Clin. Med. **26**:1934 (Sept.) 1941. (*h*) Kagan, B. M.: Studies on the Clinical Significance of the Serum Proteins: I. The Protein Content of Normal Human Venous and Capillary Serum and Factors Affecting the Accuracy of Its Determination, ibid **27**:1457 (Aug.) 1942. (*i*) Atchley, J.; Bacon, R.; Curran, G., and David, K.: A Clinical Evaluation of the Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, ibid. **30**:830 (Oct.) 1945. (*j*) Hynes, M., and Lehmann, H.: The Accuracy of Haemoglobin Determination by the Copper Sulfate-Blood Gravity Method in Indian Soldiers, J. Physiol. **104**:30P (Jan.) 1946. (*k*) Meyer, F. L.; Abbott, W. F.; Allison, M., and McKay, C.: Comparison of Plasma Protein Concentration, Hemoglobin and Hematocrit Values Determined by Chemical Methods and Calculated from Specific Gravity, Arch. Biochem. **12**:359 (March) 1947.

14. (*a*) Zozaya, J.: A Physiochemical Study of Blood Sera, J. Biol. Chem. **110**:599 (Aug.) 1935. (*b*) Looney, J. M.: The Relation Between Specific Gravity of Blood Serum and Its Protein Concentration, J. Lab. & Clin. Med. **27**:1463 (Aug.) 1942.

15. All errors given in this paper are standard errors.

differences between two determinations of hemoglobin content, the variation about a mean value for hemoglobin content. Thus, the standard deviation about the mean equals $\frac{\pm 0.22}{\sqrt{2}}$, or ± 0.156 Gm., and 95 per cent of the values might be expected to fall within twice the standard deviation (± 0.31 Gm.) or, at an assumed mean of 13 Gm. per hundred cubic centimeters, within ± 2.4 per cent of the mean. The last value, then, is an estimate at a fiducial limit of 0.95 of the error in determination of hemoglobin concentration by the method of observed differences in specific gravity.

Similar treatment of the differences in 191 duplicate estimations of plasma protein contents gave a mean difference of $+0.003 \pm 0.015$ Gm. per hundred cubic centimeters when the mathematical sign of the differences was taken into consideration. The standard deviation was ± 0.20 Gm.; again, if twice the standard deviation were taken as indicating the significant limits of variability, 95 per cent of the differences might be expected to fall within 0.40 Gm. per hundred cubic centimeters. Again, the 95 per cent expected variation about a mean plasma protein value was $\frac{\pm 0.40}{\sqrt{2}} = \pm 0.28$ Gm., or within ± 3.7 per cent of a mean of 7.5 Gm. per hundred cubic centimeters. When one again assumes a fiducial limit of 0.95, ± 3.7 per cent is an estimate of the error in determination of plasma protein content by the method of observed differences in specific gravity.

Hematocrit Reading.—All hematocrit readings were made with Wintrobe tubes,[16] utilizing oxalated venous blood. The tubes were centrifuged routinely for one hour at 3,300 revolutions per minute in a centrifuge with a radius of 15 cm. from the midpoint of the hematocrit tube, or at 4,000 revolutions per minute in a centrifuge with a radius of 10 cm. from the midpoint of the tube. This resulted in equal centrifugal force in the two centrifuges.[17] The buffy coat layer was not included in the reading. In an attempt to evaluate the personal error involved in reading the hematocrit, duplicate readings were made by two independent technicians in 192 cases. Statistical analysis of the results, taking the mathematical sign of the differences into consideration, revealed that there was a slight systematic variation between the work of the two technicians. The mean difference was -0.082 ± 0.017 cc. per hundred cubic centimeters, a systemic error of only 0.18 per cent at a mean of 45.0 cc. per hundred cubic centimeters. The standard deviation of the frequency distribution of the differences was ± 0.24 per cent, and 95 per cent of the absolute differences might be expected to be within 0.48 per cent. The 95 per cent level of variability about a mean is given by the calculation $2 \times \frac{0.24}{\sqrt{2}}$, or ± 0.34 per cent, this variability being due to the error involved in the reading of a hematocrit. Therefore, at a mean of 45 per cent and a fiducial limit of 0.95, this error is estimated at 0.76 per cent. Moreover, the error has been shown to be systematic; on the average, one technician read slightly, but significantly, higher than the other.

In the attempt to evaluate the error in the hematocrit readings due to differences in tubes and to the personal error introduced by a single observer,

16. Wintrobe, M. M.: Clinical Hematology, ed. 25, Philadelphia, Lea & Febiger, 1946.

17. International Centrifuge Catalogue, 1944.

fifty-two determinations were made on the same blood, utilizing fifty-two different tubes, all of which were read by the same person. The mean hematocrit reading in this experiment was 47.84 per cent, with a standard deviation of ± 0.27 per cent. This indicates that 95 per cent of observations might be expected to fall within ± 0.54 per cent (twice the standard deviation), or ± 1.13 per cent of the mean.

The variance due to the error involved in reading a hematocrit has been estimated at $\overline{0.17}^2$, or 0.0289, per cent. The variance due to this source of error plus the error introduced by the use of different tubes has been estimated at $\overline{0.27}^2$, or 0.0729, per cent. The difference between these two variances, or 0.0440 per cent, is a rough estimate of the variance introduced by differences in hematocrit tubes. The latter source of error, therefore, appears to outweigh the personal error.

Determination of Cell Constants.—The cell constants, mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration, were routinely calculated in the usual manner.[18] A preliminary discussion of the error involved in the determination of these ratios and of the variability of normal values seems indicated at this point.

The normal mean cell volume for healthy adults is commonly stated to be 87 cubic microns and the normal range from 82 to 92 cubic microns.[19] The mean has been confirmed, but the basis on which the normally accepted range rests is probably less secure. Pearson,[20] in 1897, reported an equation for the standard deviation of a ratio of two variables where the coefficient of variation of the numerator and denominator and the degree of correlation between them are known:

$$\text{S.D.}_{\frac{y}{x}} = \frac{\bar{y}}{\bar{x}}\sqrt{v_x^2 + v_y^2 - 2r_{xy}v_x v_y}$$

in which $\text{S.D.}_{\frac{y}{x}}$ is the standard deviation of the ratio $\frac{y}{x}$, $\bar{x}$ is the mean of the first variable, x, $\bar{y}$ is the mean of the second variable, y, v_x and v_y are the coefficients of variation of the two variables, x and y, expressed as simple proportions rather than as percentages, and r_{xy} is the coefficient of correlation of x and y.

One may assume, for the moment, that one is dealing with a single sample of blood and that repeated erythrocyte counts and hematocrit determinations have been made. In this instance r is zero, since separate subsamples are used for the determinations. The coefficients of variation due to error inherent in the procedures have been estimated in the foregoing paragraphs. Applying

18. Wintrobe, M. M.: (*a*) [11b]; (*b*) [16]; (*c*) Direct Calculation of the Volume and Hemoglobin Content of the Erythrocyte, Am. J. Clin. Path. **1**:147 (March) 1931.

19. Wintrobe, M. M.: (*a*) [16]; (*b*) [18c]; (*c*) Wintrobe, M. M.: Blood of Normal Men and Women, Bull. Johns Hopkins Hosp. **53**:118 (Sept.) 1933; Anemia, Arch. Int. Med. **54**:256 (Aug.) 1934.

20. Pearson: On a Form of Spurious Correlation Which May Arise when Indices Are Used in the Measurement of Organs, Proc. Roy. Soc. London **60**:489, 1897.

these data to the preceding equation, the expected variation in the mean cell volume can be calculated. Assuming a single estimate of the erythrocyte count ($v_x = 0.078$), a single hematocrit determination ($v_y = 0.0057$), and single values for the mean ($\bar{x} = 5{,}000{,}000$ cells per cubic millimeter and $\bar{y} = 43.5$ per cent) the computation is:

$$S.D._{\frac{y}{x}} = \frac{43.5}{5.00} \times 10\sqrt{(0.078)^2 + (0.0057)^2}$$

$$= 87 \sqrt{61.16 \times 10^{-4}}$$

$$= \pm 87\ (7.82 \times 10^{-2})$$

$$= \pm 6.8 \text{ cubic microns.}^{21}$$

This value signifies that in a single sample of blood, with means as just assumed, 95 per cent of the determined values for mean cell volume may be expected to fall within a range of twice the standard deviation, or 73.4 to 100.6 cubic microns. The utilization of the average of duplicate erythrocyte counts and hematocrit determinations in the calculation of the values for mean cell volume would reduce the variation to $\frac{S.D._{\frac{y}{x}}}{\sqrt{2}}$, or $\pm$ 4.8 cubic microns and thereby reduce the range for 95 per cent of the values to 77.4 to 96.6 cubic microns. The utilization of the average of additional determinations in a similar manner would reduce the error further, in the proportion of $\frac{1}{\sqrt{n}}$, in which n is the number of determinations averaged.

One may now consider a population of normal men, for whom the mean erythrocyte count is 5,500,000 cells per cubic millimeter, the mean hematocrit reading is 47.8 per cent and the respective standard deviations, based on duplicate determinations, are $\pm$ 380,000 cells and $\pm$ 3.0 per cent. (These standard deviations are only an estimate and serve here simply as an illustrative assumption. The literature shows considerable variation from investigator to investigator.[22] Simi-

21. The constant 10 is introduced in order that the result may be expressed in cubic microns.

22. (*a*) Ashworth and Adams.[13g] (*b*) Wintrobe.[19c] (*c*) Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, Arch. Int. Med. **43**:96 (Jan.) 1929. (*d*) Wintrobe, M. M.: Blood of Normal Young Women Residing in a Subtropical Climate, ibid. **45**:287 (Feb.) 1930. (*e*) Foster, P. C., and Johnson, J. R.: Oxygen Capacity and Hemoglobin Content of Normal Blood of Men, Proc. Soc. Exper. Biol. & Med. **28**:929 (June) 1931. (*f*) Walters, O. S.: Normal Erythrocyte, Hemoglobin, and Packed Cell Volume Standards in Young Men, J. Lab. & Clin. Med. **19**:851 (May) 1934. (*g*) Linneberg, L. L., and Schartum-Hansen, H.: Hemoglobin Content of Blood and Number and Volume of Red Blood Corpuscles in Healthy Men and Women, Norsk mag. f. lægevidensk. **96**:832 (Aug.) 1935. (*h*) Price-Jones, C.; Vaughn, J. M., and Goddard, H. M.: Hematological Standards of Healthy Persons, J. Path. & Bact. **40**:503 (May) 1935. (*i*) Osgood, E. E.: Normal Hematological Standards, Arch. Int. Med. **56**:849 (Nov.) 1935. (*j*) Belk, P.; Curtis, E., and Wilson, M.: Erythrocyte Counts, Hemoglobin and Erythrocyte Volume in Normal Young Men and Women

(Footnote continued on next page)

larly, the variability of hemoglobin concentration in a sample of healthy men may be estimated as ± 0.90 Gm., at a mean of approximately 16 Gm. per hundred cubic centimeters. This standard deviation for the erythrocyte count of a population is only slightly greater than Berkson's standard deviation for repeated duplicate determinations on the same sample. The discrepancy between theory and "observation" may well be a result of the sampling bias introduced by the probably not infrequent statistical malpractice of repeating, because of too rigid criteria of acceptability, those counts which look "off" and then accepting only those which appear more "reasonable," discarding the "off" counts as errors in technic, when actually they may well be chance variations.) These values would have corresponding coefficients of variation of 6.91 and 6.28 per cent. One may assume that the correlation coefficient between these two determinations is 0.60. (The correlation coefficient, as calculated from data appearing in the literature,[23] likewise shows considerable variation, ranging from 0.10 to 0.75. The value quoted previously is a working estimate. In the present study, the correlation coefficients for 143 male control subjects aged 15 to 30 were 0.529 for erythrocyte count and hematocrit reading, 0.569 for hemoglobin concentration and erythrocyte count, and 0.782 for hematocrit reading and hemoglobin concentration. On substitution of the aforementioned assumed values in the equation, the standard deviation of the mean cell volume is estimated to be ± 5.2 cubic microns. The mean plus or minus twice this value indicates an estimate of the range within which 95 per cent of the values of mean cell volume for the assumed population might be expected to fall. The range would be 76.6 to 97.4 cubic microns. In this instance, the utilization of additional erythrocyte counts and hematocrit readings, to calculate the mean cell volume for each person, would not reduce the variation by

$$\frac{1}{\sqrt{n}}$$

, but by somewhat less, for in following such a procedure one can only approach the true biologic variation.

In a similar manner, assuming approximate coefficients of variation of the hematologic determinations, as mentioned previously, one can calculate the expected ranges of the other cell constants, mean cell hemoglobin and mean cell hemoglobin concentration. For determinations on a single blood sample, then, the means and

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Residing in the Eastern United States, Am. J. Clin. Path. **6**:487 (Sept.) 1936. (*h*) Hamre, C. J., and Wong, K. K. L.: Hematologic Values for Normal Children Three, Four and Five Years of Age Living in Hawaii, Am. J. Dis. Child. **60**:22 (July) 1940. (*l*) Hamre, C. J., and Wong, K.: A Survey of Hemoglobin and Blood Cell Levels of Pre-School Children, Special Publication 34, Hawaii Academy of Science, 1940. (*m*) Hamre, C. J., and Au, M. H.: Hematologic Values for Normal Healthy Men Sixteen to Twenty-Five Years of Age, J. Lab. & Clin. Med. **27**:1231 (July) 1942. (*n*) Heath, C. W.: The Hemoglobin of Healthy College Under-Graduates and Comparisons with Various Medical, Social, Physiologic and Other Factors, Blood **3**:566 (May) 1948. (*o*) Valentine, W. N., and Neel, J. V.: A Statistical Study of the Variables in Subjects with Thalassemia Minor, Am. J. M. Sc., to be published. (*p*) Price-Jones, C.: The Concentration of Hemoglobin in Normal Human Blood, J. Path. & Bact. **34**:779 (Nov.) 1931. (*q*) Myers, V. C., and Eddy, H. M.: The Hemoglobin Content of Human Blood, J. Lab. & Clin. Med. **24**:502 (Feb.) 1939.

23. Wintrobe and Miller.[22c] Foster and Johnson.[22e] Walters.[22f] Linneberg and Schartum-Hansen.[22g] Belk, Curtis and Wilson.[22j]

standard deviations are 29.0 ± 2.3 micromicrograms for mean cell hemoglobin and 34 ± 0.45 per cent for mean cell hemoglobin concentration, utilizing single hematologic determinations in computation of the ratios. The standard deviations would be reduced by $\frac{1}{\sqrt{2}}$ if the average of duplicate determinations were employed in the computation.

One may assume that in the case of a population sample, the correlation coefficient between erythrocyte count and hemoglobin concentration and between hemoglobin concentration and hematocrit reading is 0.60, and that standard deviations for the population are as previously mentioned (erythrocyte count, ± 380,000 cells; hemoglobin cencentration, ± 0.90 Gm., and hematocrit reading, ± 3.0 per cent), thus giving, at their respective means, coefficients of variation of 6.91 per cent, 5.62 per cent and 6.28 per cent. In a normal population, then, the ranges of variability of 95 per cent of values about the means of the mean cell hemoglobin and mean cell hemoglobin concentration become 29.0 ± 3.4 micromicrograms and 34 ± 3.6 per cent, respectively.

By utilizing the averages of repeated determinations for each person, one can only approach the true biologic variation.

Differential Count.—Blood films were prepared from free-flowing capillary blood by the cover slip technic. The prepared films were routinely stained with Wright's stain. The differential counts were made only by physicians. Two hundred or more consecutive cells were differentiated. All films were checked by one of us (J. V. N. or F. M. S.), and in cases of apparent discrepancies, additional cells were differentiated and averaged with the previous differential count.

The question of the error involved in the differential count, expressed as a percentage, received adequate treatment by Goldner and Mann.[24] They stated the belief that the greatest error was the statistical error of sampling and that the variability could, in spite of skewness of distribution in case of means on either side of 50.0 per cent, be estimated with reasonable accuracy by the formula for the standard deviation of a percentage. The formula is $S.D. = \sqrt{\frac{pq}{n}}$, where n is the number of cells counted, p is the estimate of the mean percentage of the cell in question and q is $100 - p$. Thus, at a mean neutrophil count of 60 per cent, based on the differentiation of 200 cells, $S.D. = \sqrt{\frac{60 \times 40}{200}} = \pm 3.46$ per cent, and 95 per cent of successive differential counts on 200 cells of this blood might be expected to fall within ± 6.9 per cent of the mean of 60 per cent. Ponder and others [11e] stated that a considerable portion of the error in differential counts depended on the technics of preparation.

Reticulocyte Count.—Reticulocytes were stained vitally by the method described by Osgood and Wilhelm.[25] Smears were then prepared in the usual manner and counterstained with Wright's stain. The number of reticulocytes per 3,000 erythrocytes was counted in each case and the percentage computed.

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24. Goldner, F. M., and Mann, W. M.: The Statistical Error of the Differential White Count, Guy's Hosp. Rep. **88**:54 (Jan.) 1938.

25. Osgood, E. E., and Wilhelm, M. M.: Reticulocytes, J. Lab. & Clin. Med. **19**:1129 (July) 1934.

The variation involved in the estimates of reticulocytes on a percentage basis (not in absolute number, since this would likewise involve the error of estimation in the erythrocyte count) may probably be assumed to follow the gaussian curve of error in a manner similar to that of the error in the differential counts. If such is the case, limits of variability for 95 per cent of values may be estimated at $2\sqrt{\frac{1 \times 99}{3{,}000}}$, or ± 0.36 per cent, at a mean of 1 per cent and with the count based on a total of 3,000 cells.

Laboratory Checks.—Further to insure the reliability of our hematologic procedures, from time to time during the course of the study a 10 cc. sample of venous blood was drawn from a subject, unknown to the staff of technicians. The sample was divided into two of the usual 5 cc. portions and treated in the laboratory as

TABLE 1.—*Mean Hematologic Values and Standard Deviations in United States Army Personnel*

Observation *	Number of Subjects	Mean and Standard Error	Standard Deviation
Erythrocyte count	25	5,674,000 ± 114,000	± 570,000
Hemoglobin concentration	25	15.97 ± 0.19	± 0.93
Hematocrit reading	25	47.94 ± 0.50	± 2.50
Mean cell volume	25	89.9 ± 1.4	± 7.0
Mean cell hemoglobin	25	29.5 ± 0.4	± 2.0
Mean cell hemoglobin concentration	25	33.4 ± 0.3	± 1.4
Leukocyte count	24	8,084 ± 481	± 2,359
Neutrophils	18	60.6 ± 1.8	± 7.7
Lymphocytes	18	30.3 ± 1.5	± 6.5
Monocytes	18	6.0 ± 0.6	± 2.6
Eosinophils	18	2.8 ± 0.4	± 1.9
Plasma protein value	25	7.06 ± 0.08	± 0.38

* In this and subsequent tables, erythrocyte count is expressed in cells per cubic millimeter; hemoglobin concentration, in grams per hundred cubic centimeters; hematocrit reading, in per cent; mean cell volume, in cubic microns; mean cell hemoglobin, in micromicrograms; mean cell hemoglobin concentration, in per cent; leukocyte count, in cells per cubic millimeter; differential count values, in per cent, and plasma protein values, in grams per hundred cubic centimeters.

the blood of 2 individual subjects. Analysis of the differences in fifteen such tests indicated variations within the limits of error of the technics.

CONTROL STUDIES ON AMERICANS

The mean values and respective standard deviations for the various hematologic procedures performed on 25 United States Army volunteers are presented in table 1. The subjects formed a group of healthy young men who had a rather heterogeneous racial background. For instance, the series included second generation Japanese and Chinese. Hamre and others [22k-m] found no significant racial differences in the cellular elements of the blood in persons in the Hawaiian islands, having studied the problem rather extensively in a variety of age groups.

It may be noted in table 1 that the mean values for the various hematologic determinations agree with the usually accepted means.[14a] The variabilities about the means, however, are somewhat higher than the usual standards. This question of acceptable variability has been discussed and will be returned to again near the end of this report.

TABLE 2.—*Over-All Comparison of Hematologic Differences Between Subjects in Hiroshima and Those in Kure*

Observation	Subjects in Kure			Subjects in Hiroshima			Difference ± Error of Difference †	Value for t ‡	Value for F Test §	No. of Pairs	Mean Difference and Standard Error	Value for t
	No. of Observations	Mean and Standard Error	Standard Deviation	No. of Observations	Mean and Standard Error	Standard Deviation						
Erythrocyte count	709	4,604,000 ±17,000	±442,000	629	4,521,000 ±20,000	±501,000	**+83,000 ±26,000¶**	3.2	1.29	437	**+65,000 ±27,000**	**2.4**
Hemoglobin concentration	912	13.14 **± 0.041**	±1.25	872	12.84± **0.040**	±1.34	**+0.30 ±0.061**	4.9	1.15	447	**+0.26± 0.075**	3.5
Hematocrit reading	802	41.46± 0.13	±3.60	757	40.98± 0.14	±3.73	**+0.48 ±0.19**	2.5	1.08	...	.....	...
Mean cell volume	629	87.85± **0.28**	±6.90	546	88.34 ±0.30	±7.26	−0.49 ±0.41	1.2	1.11	...	.....	...
Mean cell hemoglobin	708	**28.74± 0.088**	±2.34	627	28.55± 0.14	±2.59	+0.19 ±0.16	1.2	1.23	433	**+0.21 ±0.13**	1.6
Mean cell hemoglobin concentration	685	32.15 ± 0.053	±1.37	757	32.20± 0.052	±1.43	−0.05 ±0.074	0.7	1.09	...	.....	...
Plasma protein value	912	7.59 ± 0.017	±0.500	872	7.65 ± 0.019	±0.549	**−0.06± 0.025**	2.4	1.21	443	−0.021 **±0.028**	0.8
Leukocyte count	707	9,903± 101	±2,693	645	9,847± 122	±3,100	+ 56 ±160	0.4	1.32	455	+ 20 ±170	0.1
Neutrophils	707	54.96 ± 0.35	±9.35	637	54.96± 0.39	±9.94	0.00 ±0.53	0.0	1.13	432	−0.59 **±0.64**	0.9
Lymphocytes	707	29.40 ± 0.28	±7.54	637	28.01 ± 0.31	±7.89	**+1.39 ±0.42**	3.5	1.10	432	**+2.02 ±0.48**	4.2
Monocytes	707	6.36 ± 0.085	±2.26	637	6.33 ± 0.093	±2.35	+0.03 ±0.13	0.2	1.08	432	+0.02 ±0.14	0.1
Eosinophils	707	8.93 **± 0.26**	±7.02	637	10.76 ± 0.32	±7.97	**−1.83 ±0.41**	4.5	1.29	432	**−0.99± 0.47**	2.1
Reticulocyte count *	133	0.89 ± 0.03	±0.38	120	0.96 ± 0.04	±0.49	−0.07 ±0.05	1.4	1.72	...	.....	...

* In this and subsequent tables, reticulocyte count is expressed in per cent of erythrocytes.

† In this and subsequent tables, differences carrying a plus sign indicate a higher value for control subjects and those carrying a minus sign, a higher value for epilated subjects.

‡ Values for t in excess of 2.0 indicate differences significant at the probability level of 95 per cent; values in excess of 2.6, differences significant at the 99 per cent probability level.

§ Values for F in excess of 1.16 indicate differences significant at the probability level of 95 per cent; values in excess of 1.24, differences significant at the 99 per cent probability level.

¶ In this and subsequent tables, differences greater than twice their errors are indicated with bold face type.

STATISTICAL PROCEDURES

Although every effort was made to establish two subpopulations within the cities of Kure and Hiroshima comparable in all respects except exposure to an atomic bombing, there existed within each of these two populations considerable hematologic variability, introduced by such well recognized factors as age and sex. Comparison of the two populations in terms of the means and the standard error of the difference is a relatively crude statistical procedure, since in these circumstances the standard error of the means, on which the evaluation of the significance of any observed difference rests, receives a substantial contribution of variation from the aforementioned factors, which are of no particular interest in the present study. In order to refine the comparison of the two groups, each epilated person was paired at random with a control subject of the same sex and of similar age. The differences between the corresponding hematologic values of these pairs were then treated statistically. Once pairs had been established, the same pairs were retained for all subsequent analysis. Since only those persons who had been seen twice were included in this paired series, the total number of pairs which could be established was far less than the number of observations, so that this procedure, while inherently more sensitive, entailed sacrificing a considerable number of observations. However, the procedure did avoid, in part, the necessity of establishing multiple regression equations for adequate comparison of the two groups. It was felt that the survey was not sufficiently complete, in many respects, to justify treatment of the data by the more elaborate analysis of covariance.

PRESENTATION OF DATA

Over-All Blood Picture.—Table 2 presents the mean, standard deviation, and standard error of the mean for all the hematologic determinations carried out in Hiroshima and Kure, as well as a summary of the gross differences between subjects in the two cities. These differences are expressed in two ways, first as the differences between the means of the various determinations carried out in the two cities, and secondly as the mean differences between the series of the aforementioned paired individual subjects. In both methods, the t statistic was used to evaluate the significance of any observed difference. With samples of this size, any value of t in excess of 2.0 indicates a difference significant at the 95 per cent probability level, whereas a value in excess of 2.6 denotes a difference significant at the 99 per cent probability level. Differences greater than twice their errors, corresponding to a t value in excess of 2.0, are printed in bold face type in all tables. Differences are listed with an arithmetical sign, + indicating a higher value for controls, and — indicating a higher value for epilated persons.

Because most of the hematocrit determinations were made during the latter part of the study, there were not sufficient duplicate observations on the same persons to warrant an analysis by differences of the established pairs, a fact which resulted in the omission also of the analysis of mean cell volume and mean cell hemoglobin concentration by this method. The small number of reticulocyte counts likewise did not justify an analysis of the differences of established pairs. These omissions are also evident in subsequent tables.

A number of interesting facts emerge from a study of table 2:

1. Determinations of erythrocyte count and hemoglobin concentration, by both types of analysis, were slightly lower in Hiroshima than in Kure. Hematocrit

values were also lower in Hiroshima. These differences are of statistical significance. There is, on the other hand, no significant difference with respect to differences in mean cell volume, mean cell hemoglobin or mean cell hemoglobin concentration. The differences between the two series, epilated subjects and control subjects, thus apear to be quantitative rather than qualitative. However, a discussion of standard deviations appears later in this report.

2. Leukocyte levels were practically identical in the two cities and were probably on the high side by American standards. However, there appeared to be slight differences in the percentage values for some of the various types of leukocytes. By comparison with Kure, the number of lymphocytes showed an absolute depression of 1.39 per cent in Hiroshima, and the number of eosinophils was elevated by 1.83 per cent. These differences, although small, are statistically significant.

3. Plasma protein values were slightly higher in Hiroshima than in Kure, but the significance of the difference is problematic. In both cities, plasma protein values were slightly elevated by American standards.

4. For every hematologic characteristic studied, the standard deviation was larger in Hiroshima than in Kure. Taken singly, these differences are not striking. However, because of the large numbers involved, they are, in several cases, statistically significant, as indicated by the F test, on which data are included in table 2.[26] With the number of degrees of freedom involved here, a value of F in excess of 1.16 indicates a difference significant at the 95 per cent probability level and one in excess of 1.24 exceeds a 99 per cent probability level. Six of the thirteen values exceed the 95 per cent level and four of these, the 99 per cent level. Moreover, the facts that the differences are, in all instances, in the same direction and that the value for F, in all instances, exceeds 1.08 are of themselves of great significance. It may be concluded that the Hiroshima population studied was hematologically more variable than that studied in Kure.

There were, then, a number of slight, yet statistically significant, differences between the peripheral hematologic pictures in the two cities. The appreciation of the meaning of these differences can perhaps be furthered through additional analysis of the data with respect to these questions:

1. Is there evidence that any particular age or sex group contributed disproportionately to the observed differences?

2. Is there evidence that the traumatic injuries and flash burns which were so frequent and severe in Hiroshima played a role in the hematologic difference?

3. Is there evidence that the amount of radiation over and beyond the minimal epilating dose, as estimated by distance from the hypocenter of the explosion, extent of epilation or degree of severity of radiation sickness, influenced the final picture?

Relation Between Age and Sex and Response to Atomic Bombing.—A breakdown of the results of hematologic observations on the control and epilated groups, with respect to age and sex, is given in tables 3 and 4. Data are not distinguished with respect to sex at ages below 14. Although the control figures on normal Japanese subjects bring out the number of facts of general hematologic interest,

26. Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology, ed. 4, Ames, Iowa, Iowa State College Press, 1946.

TABLE 3.—*Relation Between Age and Sex and Hematologic Findings in*

Observation	Age, Years *	Subjects in Kure: Male Number	Male Mean and Standard Error	Male Standard Deviation	Female Number	Female Mean and Standard Error	Female Standard Deviation
Erythrocyte count	0-9	99	4,714,000 ± 38,000	±0.378	...	.....	.....
	10-14	111	4,646,000 ± 32,000	±0.340	...	.....	.....
	15-19	101	4,882,000 ± 37,000	±0.368	84	4,633,000 ± 52,000	±368,000
	20-39	52	4,804,000 ± 53,000	±0.383	95	4,386,000 ± 48,000	±466,000
	40 and above	90	4,562,000 ± 48,000	±0.457	77	4,188,000 ± 42,000	±372,000
Hemoglobin concentration	0-9	136	12.65 ± 0.080	±0.93	...	.....	.....
	10-14	187	12.86 ± 0.063	±0.86	...	.....	.....
	15-19	118	14.19 ± 0.105	±1.14	157	12.96 ± 0.080	±1.00
	20-39	51	14.45 ± 0.122	±0.87	96	12.59 ± 0.126	±1.24
	40 and above	90	13.94 ± 0.140	±1.33	77	12.26 ± 0.132	±1.16
Hematocrit reading	0-9	119	39.11 ± 0.22	±2.41	...	.....	.....
	10-14	171	39.93 ± 0.15	±2.00	...	.....	.....
	15-19	116	44.05 ± 0.32	±3.40	137	40.93 ± 0.23	±2.74
	20-39	44	46.14 ± 0.45	±2.96	77	40.67 ± 0.40	±3.55
	40 and above	74	45.08 ± 0.43	±3.69	64	39.88 ± 0.43	±3.47
Mean cell volume	0-9	95	83.23 ± 0.55	±5.35	...	.....	.....
	10-14	109	85.06 ± 0.55	±5.76	...	.....	.....
	15-19	99	88.15 ± 0.64	±6.34	67	86.88 ± 0.76	±6.19
	20-39	44	91.00 ± 0.89	±5.88	77	89.08 ± 0.80	±7.06
	40 and above	74	93.22 ± 0.82	±7.09	64	90.13 ± 0.75	±6.04
Mean cell hemoglobin	0-9	99	26.85 ± 0.18	±1.76	...	.....	.....
	10-14	111	27.68 ± 0.18	±1.91	...	.....	.....
	15-19	101	29.25 ± 0.19	±1.89	84	28.24 ± 0.22	±1.97
	20-39	51	30.17 ± 0.27	±1.94	95	28.75 ± 0.25	±2.40
	40 and above	90	30.67 ± 0.22	±2.12	77	29.36 ± 0.25	±2.20
Mean cell hemoglobin concentration	0-9	105	32.28 ± 0.13	±1.35	...	.....	.....
	10-14	130	32.24 ± 0.09	±1.07	...	.....	.....
	15-19	99	32.49 ± 0.14	±1.35	73	31.94 ± 0.14	±1.22
	20-39	43	32.55 ± 0.25	±1.62	77	31.76 ± 0.17	±1.48
	40 and above	75	31.99 ± 0.19	±1.64	64	31.87 ± 0.17	±1.37
Leukocyte count	0-9	100	12,570 ± 312	±3,124	...	.....	.....
	10-14	112	9,973 ± 206	±2,177	...	.....	.....
	15-19	101	9,926 ± 245	±2,467	84	9,655 ± 262	±2,402
	20-39	52	8,942 ± 277	±1,996	95	9,415 ± 267	±2,607
	40 and above	88	9,284 ± 240	±2,251	75	8,500 ± 228	±1,972
Neutrophils	0-9	100	48.80 ± 0.82	±8.19	...	.....	.....
	10-14	112	50.36 ± 0.79	±8.35	...	.....	.....
	15-19	101	54.78 ± 0.79	±7.96	84	61.19 ± 0.87	±7.98
	20-39	52	56.83 ± 1.22	±8.78	95	57.13 ± 0.94	±9.21
	40 and above	88	57.11 ± 1.05	±9.97	75	56.48 ± 0.90	±7.83
Lymphocytes	0-9	100	32.89 ± 0.70	±6.98	...	.....	.....
	10-14	112	33.21 ± 0.75	±7.89	...	.....	.....
	15-19	101	28.14 ± 0.56	±5.67	84	25.96 ± 0.72	±6.60
	20-39	52	26.59 ± 0.94	±6.79	95	27.09 ± 0.67	±6.66
	40 and above	88	28.89 ± 0.90	±8.53	75	30.53 ± 0.81	±7.02
Monocytes	0-9	100	6.57 ± 0.21	±2.08	...	.....	.....
	10-14	112	6.20 ± 0.18	±1.89	...	.....	.....
	15-19	101	6.64 ± 0.23	±2.36	84	5.70 ± 0.22	±2.03
	20-39	52	6.29 ± 0.25	±1.79	95	6.30 ± 0.24	±2.37
	40 and above	88	6.88 ± 0.32	±3.02	75	6.17 ± 0.23	±2.03
Eosinophils	0-9	100	11.58 ± 0.79	±7.89	...	.....	.....
	10-14	112	10.07 ± 0.67	±7.09	...	.....	.....
	15-19	101	10.49 ± 0.78	±7.91	84	7.51 ± 0.60	±5.51
	20-39	52	10.48 ± 1.16	±8.37	95	9.60 ± 0.76	±7.52
	40 and above	88	7.06 ± 0.45	±4.24	75	6.91 ± 0.55	±4.83
Plasma protein value	0-9	136	7.46 ± 0.04	±0.48	...	.....	.....
	10-14	187	7.49 ± 0.04	±0.50	...	.....	.....
	15-19	118	7.64 ± 0.04	±0.46	157	7.69 ± 0.04	±0.48
	20-39	51	7.5 ± 0.08	±0.57	96	7.78 ± 0.05	±0.48
	40 and above	90	7.57 ± 0.05	±0.48	77	7.70 ± 0.06	±0.53
Reticulocyte count	0-9	7	0.84 ± 0.14	±0.37	...	.....	.....
	10-14	11	0.85 ± 0.09	±0.31	...	.....	.....
	15-19	25	0.73 ± 0.06	±0.28	28	1.10 ± 0.05	±0.29
	20-39	15	1.11 ± 0.10	±0.40	14	0.92 ± 0.11	±0.41
	40 and above	16	0.75 ± 0.08	±0.32	17	0.72 ± 0.07	±0.28

* In this and the subsequent table, data for subjects under 14 are not differentiated according to sex.

Control and Epilated Subjects: Mean Values and Differences Between Means

Subject in Hiroshima						Mean Difference ± Standard Error	
Male			Female				
Number	Mean and Standard Error	Standard Deviation	Number	Mean and Standard Error	Standard Deviation	Male Subjects	Female Subjects
85	4,676,000 ± 38,000	±346,000	...	.....	.....	+ 38,000 ± 54,000	.....
79	4,682,000 ± 39,000	±346,000	...	.....	.....	− 36,000 ± 50,000	.....
94	4,898,000 ± 46,000	±447,000	72	4,464,000 ± 41,000	±346,000	− 16,000 ± 59,000	**+169,000 ± 66,000**
46	4,813,000 ± 72,000	±490,000	106	4,223,000 ± 43,000	±447,000	− 9,000 ± 89,000	**+163,000 ± 64,000**
74	4,408,000 ± 61,000	±529,000	73	4,081,000 ± 48,000	±410,000	+154,000 ± 78,000	+107,000 ± 64,000
127	12.34 ± 0.077	±0.87	...	.....	.....	**+0.31 ± 0.12**	.....
150	12.55 ± 0.082	±1.00	...	.....	.....	**+0.31 ± 0.10**	.....
140	13.73 ± 0.112	±1.32	155	12.78 ± 0.084	±1.05	**+0.46 ± 0.15**	+0.18 ± 0.12
47	14.47 ± 0.193	±1.32	107	12.21 ± 0.118	±1.22	−0.02 ± 0.23	**+0.38 ± 0.17**
73	13.39 ± 0.165	±1.41	73	12.03 ± 0.155	±1.32	**+0.55 ± 0.22**	+0.23 ± 0.20
120	38.63 ± 0.23	±2.53	...	.....	.....	+0.48 ± 0.32	.....
143	39.35 ± 0.25	±3.00	...	.....	.....	**+0.58 ± 0.29**	.....
135	43.28 ± 0.30	±3.46	122	40.78 ± 0.24	±2.65	+0.77 ± 0.44	**+0.15 ± 0.33**
36	46.00 ± 0.51	±3.04	85	40.24 ± 0.38	±3.46	+0.14 ± 0.67	+0.43 ± 0.55
57	43.90 ± 0.56	±4.20	59	39.86 ± 0.44	±3.39	+1.18 ± 0.71	+0.02 ± 0.62
81	83.40 ± 0.56	±5.00	...	.....	.....	−0.17 ± 0.78	.....
77	84.40 ± 0.60	±5.29	...	.....	.....	+0.66 ± 0.81	.....
90	84.18 ± 0.60	±5.66	62	88.13 ± 0.72	±5.66	**+3.97 ± 0.88**	−1.25 ± 1.06
36	91.33 ± 0.94	±5.66	84	90.57 ± 0.82	±7.48	−0.33 ± 1.29	−1.49 ± 1.55
57	94.72 ± 0.96	±7.21	59	92.39 ± 1.01	±7.75	−1.50 ± 1.26	−2.26 ± 1.26
85	26.76 ± 0.24	±2.24	...	.....	.....	+0.09 ± 0.30	.....
79	27.17 ± 0.23	±2.00	...	.....	.....	+0.51 ± 0.29	.....
94	28.23 ± 0.23	±2.24	71	28.65 ± 0.25	±2.12	**+1.02 ± 0.30**	−0.41 ± 0.33
46	29.96 ± 0.34	±2.33	106	28.97 ± 0.24	±2.52	+0.21 ± 0.43	−0.22 ± 0.35
73	30.36 ± 0.31	±2.65	73	29.38 ± 0.30	±2.54	+0.31 ± 0.38	−0.02 ± 0.39
120	32.11 ± 0.12	±1.26	...	.....	.....	+0.17 ± 0.18	.....
143	32.09 ± 0.13	±1.50	...	.....	.....	+0.15 ± 0.16	.....
135	32.43 ± 0.13	±1.55	122	31.94 ± 0.12	±1.32	+0.06 ± 0.19	−0.00 ± 0.18
36	33.33 ± 0.17	±1.04	85	32.00 ± 0.15	±1.41	**−0.78 ± 0.30**	−0.24 ± 0.23
57	32.11 ± 0.22	±1.66	59	32.08 ± 0.16	±1.22	−0.12 ± 0.29	−0.21 ± 0.23
87	12,305 ± 386	±3,606	...	.....	.....	+ 270 ± 500	.....
79	11,791 ± 363	±3,226	...	.....	.....	**−1,820 ± 420**	.....
95	10,394 ± 303	±2,956	84	9,338 ± 267	±2,449	− 460 ± 400	+320 ± 370
47	9,663 ± 342	±2,347	105	8,481 ± 218	±2,236	− 110 ± 440	**+940 ± 350**
73	8,555 ± 274	±2,338	75	8,233 ± 258	±2,236	+ **720 ± 360**	+270 ± 350
87	49.53 ± 1.07	±10.00	...	.....	.....	−0.73 ± 1.35	.....
79	51.19 ± 1.01	± 9.02	...	.....	.....	−0.83 ± 1.28	.....
95	52.64 ± 1.09	±10.61	84	58.13 ± 1.13	±10.31	+2.14 ± 1.35	**+3.06 ± 1.43**
45	56.58 ± 1.30	± 8.75	103	57.34 ± 0.85	± 8.66	+0.25 ± 1.78	**−0.21 ± 1.27**
71	57.76 ± 1.03	± 8.66	73	57.76 ± 0.97	± 8.29	−0.65 ± 1.47	**−1.28 ± 1.32**
87	32.14 ± 0.89	±8.29	...	.....	.....	+0.75 ± 1.13	.....
79	30.11 ± 0.89	±7.91	...	.....	.....	**+3.10 ± 1.16**	.....
95	27.46 ± 0.81	±7.91	84	26.46 ± 0.75	±6.91	+0.68 ± 0.98	−0.50 ± 1.04
45	27.08 ± 1.12	±7.48	103	26.15 ± 0.74	±7.46	−0.49 ± 1.46	+0.94 ± 1.00
71	26.64 ± 0.77	±6.51	73	28.10 ± 0.93	±7.91	+1.95 ± 1.18	**+2.23 ± 1.23**
87	6.06 ± 0.23	±2.10	...	.....	.....	+0.51 ± 0.31	.....
79	6.42 ± 0.27	±2.37	...	.....	.....	−0.22 ± 0.32	.....
95	6.30 ± 0.22	±2.17	84	5.70 ± 0.23	±2.06	+0.34 ± 0.32	−0.00 ± 0.32
45	6.63 ± 0.34	±2.29	103	6.14 ± 0.22	±2.25	−0.34 ± 0.42	+0.16 ± 0.33
71	7.20 ± 0.33	±2.75	73	6.54 ± 0.31	±2.65	−0.32 ± 0.46	−0.37 ± 0.39
87	12.08 ± 0.89	± 8.29	...	.....	.....	−0.50 ± 1.19	.....
79	12.14 ± 0.83	± 7.39	...	.....	.....	−2.07 ± 1.07	.....
95	13.93 ± 1.09	±10.61	84	9.79 ± 0.83	±7.64	**−3.44 ± 1.34**	**−2.28 ± 1.02**
45	9.34 ± 1.11	± 7.42	103	10.21 ± 0.73	±7.37	+1.14 ± 1.61	−0.61 ± 1.05
71	8.72 ± 0.66	± 5.55	73	8.34 ± 0.70	±6.04	**−1.66 ± 0.80**	**−1.43 ± 0.89**
127	7.52 ± 0.05	±0.57	...	.....	.....	−0.06 ± 0.06	.....
150	7.64 ± 0.04	±0.53	...	.....	.....	**−0.15 ± 0.06**	.....
140	7.85 ± 0.04	±0.49	155	7.78 ± 0.04	±0.53	**−0.21 ± 0.06**	−0.09 ± 0.06
47	7.63 ± 0.09	±0.59	107	7.61 ± 0.05	±0.54	−0.13 ± 0.12	**+0.17 ± 0.07**
73	7.37 ± 0.06	±0.53	73	7.63 ± 0.06	±0.50	**+0.20 ± 0.08**	+0.07 ± 0.08
11	0.92 ± 0.17	±0.56	...	.....	.....	−0.08 ± 0.22	.....
17	0.90 ± 0.10	±0.43	...	.....	.....	−0.05 ± 0.13	.....
20	0.84 ± 0.12	±0.54	16	1.38 ± 0.17	±0.68	−0.11 ± 0.13	−0.28 ± 0.18
10	1.06 ± 0.13	±0.42	18	0.95 ± 0.09	±0.37	+0.05 ± 0.16	**−0.02 ± 0.14**
14	0.79 ± 0.07	±0.25	14	0.89 ± 0.10	±0.36	−0.04 ± 0.11	**−0.17 ± 0.12**

these findings will not be discussed at this time but will be considered in another paper.[27] It is apparent from the tables that there was no clear and consistent tendency for any particular age or sex group to contribute disproportionately to the observed differences in erythrocyte count, hemoglobin content and hematocrit

TABLE 4.—*Relation Between Age and Sex and Hematologic Findings: Comparison of Mean Differences of Established Pairs, Grouped According to Age and Sex*

		Male Subjects		Female Subjects	
Observation	Age, Years	Number	Mean Difference and Standard Error	Number	Mean Difference and Standard Error
Erythrocyte count	0-9	55	+ 3,000 ± 59,000	..	.....
	10-14	55	+ 3,000 ± 69,000	..	.....
	15-19	91	− 45,000 ± 66,000	42	+110,000 ± 84,000
	20-39	31	−131,000 ± 92,000	66	+114,000 ± 81,000
	40 and above	49	**+232,000 ± 92,000**	48	**+210,000 ± 70,000**
Hemoglobin concentration	0-9	56	+0.29 ± 0.167	..	.....
	10-14	55	+0.22 ± 0.164	..	.....
	15-19	94	+0.24 ± 0.160	42	+0.24 ± 0.182
	20-39	32	−0.25 ± 0.280	68	+0.28 ± 0.221
	40 and above	51	**+0.69 ± 0.289**	49	+0.27 ± 0.250
Mean cell hemoglobin	0-9	55	+0.46 ± 0.312	..	.....
	10-14	55	+0.50 ± 0.357	..	.....
	15-19	94	**+0.71 ± 0.254**	40	−0.30 ± 0.396
	20-39	31	−0.05 ± 0.454	65	+0.04 ± 0.371
	40 and above	49	−0.13 ± 0.446	47	−0.59 ± 0.458
Leukocyte count	0-9	71	+ 218 ± 566	..	.....
	10-14	61	**−1,484 ± 499**	..	.....
	15-19	87	− 604 ± 379	39	− 64 ± 533
	20-39	29	− 155 ± 596	68	**+1,427 ± 399**
	40 and above	52	+ 320 ± 374	51	+ 500 ± 396
Neutrophils	0-9	60	−1.87 ± 1.77	..	.....
	10-14	55	−1.27 ± 1.81	..	.....
	15-19	79	−1.29 ± 1.43	37	**+4.59 ± 2.18**
	20-39	30	+0.40 ± 2.15	69	+0.14 ± 1.59
	40 and above	52	−0.85 ± 1.93	51	−2.00 ± 1.77
Lymphocytes	0-9	60	+2.33 ± 1.44	..	.....
	10-14	55	+1.55 ± 1.46	..	.....
	15-19	79	+1.76 ± 1.07	37	**+1.65 ± 1.53**
	20-39	30	+0.07 ± 1.68	69	+1.12 ± 1.15
	40 and above	52	+2.88 ± 1.47	51	**+3.90 ± 1.49**
Monocytes	0-9	60	**+0.88 ± 0.35**	..	.....
	10-14	55	−0.06 ± 0.40	..	.....
	15-19	79	+0.07 ± 0.31	37	−0.61 ± 0.42
	20-39	30	−0.43 ± 0.54	69	+0.38 ± 0.42
	40 and above	52	−0.75 ± 0.42	51	−0.15 ± 0.42
Eosinophils	0-9	60	−1.40 ± 1.60	..	.....
	10-14	55	−0.53 ± 1.15	..	.....
	15-19	79	−0.34 ± 1.23	37	**−3.86 ± 1.70**
	20-39	30	+1.33 ± 1.49	69	−0.88 ± 1.09
	40 and above	52	−0.81 ± 1.15	51	**−2.41 ± 1.18**
Plasma protein value	0-9	56	−0.09 ± 0.07	..	.....
	10-14	56	**−0.18 ± 0.08**	..	.....
	15-19	94	**−0.16 ± 0.06**	42	+0.07 ± 0.10
	20-39	32	−0.05 ± 0.09	67	**+0.18 ± 0.07**
	40 and above	49	**+0.18 ± 0.09**	49	−0.01 ± 0.08

value. Rather, the over-all difference for these determinations seems to be due to contributions from most of the groups studied. Thus, in table 4, for instance,

27. Snell, F. M.: Observations on the Hematological Values of the Japanese, to be published.

six of the eight differences in erythrocyte count and seven of the eight differences in hemoglobin content agree in sign with that for the group as a whole. There were, however, a few apparently disproportionate responses of particular sex and

TABLE 5.—*Relation Between Extent of Associated Traumatic Injury and Burns and Hematologic Findings for Epilated Persons: Comparison of Mean Values According to Extent of Injury*

Observation	Subjects in Group 1 * No.	Subjects in Group 1 * Mean and Standard Error	Subjects in Group 2 No.	Subjects in Group 2 Mean and Standard Error	Subjects in Group 3 No.	Subjects in Group 3 Mean and Standard Error
Erythrocyte count	197	4,524,000 ± 36,000	294	4,512,000 ± 29,000	89	4,574,000 ± 50,000
Hemoglobin concentration	302	12.80 ± 0.079	411	12.78 ± 0.065	105	12.96 ± 0.137
Hematocrit reading	268	40.66 ± 0.232	363	41.08 ± 0.199	93	41.41 ± 0.384
Mean cell volume	174	87.48 ± 0.525	254	88.69 ± 0.472	76	88.42 ± 0.733
Mean cell hemoglobin	196	28.44 ± 0.175	294	28.51 ± 0.157	89	28.28 ± 0.252
Mean cell hemoglobin concentration	268	32.33 ± 0.091	352	32.15 ± 0.074	93	32.07 ± 0.164
Leukocyte count	199	10,394 ± 228	296	9,689 ± 179	88	9,477 ± 319
Neutrophils	196	58.80 ± 0.736	294	54.70 ± 0.601	86	55.29 ± 1.009
Lymphocytes	196	28.16 ± 0.572	294	28.12 ± 0.461	86	27.53 ± 0.824
Monocytes	196	6.35 ± 0.163	294	6.42 ± 0.146	86	6.41 ± 0.217
Eosinophils	196	11.51 ± 0.519	294	10.94 ± 0.484	86	10.18 ± 0.894
Plasma protein value	302	7.67 ± 0.032	411	7.63 ± 0.027	105	7.64 ± 0.050
Reticulocyte count	37	0.934 ± 0.069	58	0.922 ± 0.065	17	0.874 ± 0.070

* In this and the subsequent table, group 1 indicates those persons with no injuries, or with minor burns and glass cuts; group 2, those with moderately severe first, second or third degree burns involving up to approximately 10 per cent of the body area, or with comparable other traumatic injury, and group 3, those with burns involving more than 10 per cent of the body area, or with other types of severe traumatic injury.

TABLE 6.—*Relation Between Extent of Associated Traumatic Injury and Burns and Hematologic Findings for Epilated Persons: Comparison of Mean Differences Between Established Pairs According to Extent of Injury of Epilated Subjects*

Observation	Subjects in Group 1 No.	Subjects in Group 1 Mean Difference and Standard Error	Subjects in Group 2 No.	Subjects in Group 2 Mean Difference and Standard Error	Subjects in Group 3 No.	Subjects in Group 3 Mean Difference and Standard Error
Erythrocyte count	135	+154,000 ± 51,000	214	+26,000 ± 39,000	65	−47,000 ± 65,000
Hemoglobin concentration	139	+0.46 ± 0.138	216	+0.22 ± 0.107	66	+0.23 ± 0.180
Mean cell hemoglobin	135	+0.12 ± 0.239	212	+0.22 ± 0.192	63	+0.72 ± 0.306
Leukocyte count	143	+10 ± 333	221	−20 ± 237	66	−54 ± 422
Neutrophils	133	+0.80 ± 1.133	210	−1.52 ± 0.924	66	−1.46 ± 1.668
Lymphocytes	133	+1.93 ± 0.862	210	+1.82 ± 0.716	66	+2.00 ± 1.322
Monocytes	133	−0.17 ± 0.256	210	+0.12 ± 0.220	66	+0.36 ± 0.341
Eosinophils	133	−2.20 ± 0.863	210	−0.44 ± 0.659	66	−0.61 ± 1.181
Plasma protein value	139	−0.07 ± 0.05	214	+0.22 ± 0.038	66	+0.17 ± 0.068

age groups, which, taken at their face value, are statistically significant. It should be borne in mind that on the basis of chance alone values in 5 per cent of t tests may be expected to exceed the value of 2.0. This variation also occurred in determination of the cell constants, even though there was no significant over-all tendency. The fact that the two different analytic approaches failed in many instances to yield confirming results lessens the weight to be given to these findings.

The total leukocyte count and the percentage of neutrophils and monocytes, which showed no significant gross differences in table 2, likewise showed no clearly consistent tendencies on the breakdown, although there were several minor differences which may, in the light of future research, prove significant. The decrease in percentage of lymphocytes and the increase in percentage of esinophils recorded in Hiroshima apparently occurred in groups of all ages and both sexes. Differences in plasma protein values, although statistically significant in many of the groups, fell into no simple pattern. Reticulocyte counts, likewise, showed no significant pattern.

Relation Between Traumatic Injuries and Flash Burns and Hematologic Observations.—As noted previously, many epilated subjects received, in addition to the radiation, flash burns, glass cuts and injuries from other flying debris. The possibility that the observed differences between subjects in Kure and those in Hiroshima were actually due to these associated injuries rather than to the factor of irradiation had to be explored. Accordingly, Hiroshima subjects were classified into three groups, group 1 consisting of those persons with no injuries or with minor burns and glass cuts, group 2 consisting of those with moderately severe first, second or third degree burns involving up to approximately 10 per cent of the body area, or with roughly comparable other traumatic injury, and group 3 consisting of those who received either burns of varying severity involving more than 10 per cent of the body area or other types of severe traumatic injury. The records of relatively few persons, who could not be readily classified from the available data, were not incorporated into the analysis. The mean values in these three groups, and the mean differences between the established pairs, are shown in tables 5 and 6.

The significance of the various trends shown here has been investigated by an analysis of the variance between and within groups. There was a tendency for the erythrocyte count to be higher for those subjects who received the severest injuries. This tendency is evident in both table 5 and table 6 but is statistically significant only in table 6. Moreover, inspection of tables 5 and 6 reveals that values for hemoglobin concentration and hematocrit reading tend to vary in the same manner as do those for erythrocyte count, although the trend is not statistically significant by this analysis. One faces, then, the paradox that those persons most severely burned or otherwise injured at the time of the bombing later showed a tendency to an increased number of erythrocytes, with correspondingly higher values for hemoglobin concentration and hematocrit reading. This point will be discussed further later in this report. The explanation of the over-all differences between subjects in Kure and those in Hiroshima does not lie here.

In table 5 there is indicated a tendency to a lower leukocyte count for those receiving the severest injury, but this tendency, although statistically significant in table 5, is not borne out in table 6; therefore, its validity may be questioned.

Relation Between Amount of Radiation and Hematologic Observations.—Although all the subjects in Hiroshima included in this study allegedly experienced scalp epilation, which is probably the most reliable single criterion of the absorption of large amounts of whole body radiation, there undoubtedly existed, within the group, considerable variation in the actual dose received, which may have varied from the minimal epilating dose with this type of irradiation (about 300 r) up to the maximum tolerated by a few persons (say 700 r). Moreover, it is likely that a few persons included in the study did not experience true radiation

epilation. One hundred and ninety-three of 924 persons, or 20.9 per cent of those reporting epilation, were more than 2 kilometers from the hypocenter at the time of the explosion, whereas the Joint Commission found that only 8.3 per cent of the cases of epilation which they studied in the weeks immediately following the bombing were in persons who had been beyond the 2 kilometer zone.[1] How-

TABLE 7.—*Relation Between Distance from Hypocenter and Hematologic Findings: Comparison of Mean Values According to Distance*

	Distance from Hypocenter					
	0 to 1 Km.		1 to 2 Km.		Over 2 Km.	
Observation	No.	Mean and Standard Error	No.	Mean and Standard Error	No.	Mean and Standard Error
Erythrocyte count	135	4,429,000 ± 47,000	378	4,530,000 ± 25,000	116	4,610,000 ± 44,000
Hemoglobin concentration	169	12.89 ± 0.113	518	12.85 ± 0.058	186	12.77 ± 0.096
Hematocrit reading	138	41.38 ± 0.318	440	41.07 ± 0.178	169	40.80 ± 0.298
Mean cell volume	108	89.46 ± 0.745	328	88.46 ± 0.382	108	86.69 ± 0.618
Mean cell hemoglobin	135	28.96 ± 0.265	377	28.57 ± 0.122	121	27.97 ± 0.225
Mean cell hemoglobin concentration	138	32.44 ± 0.132	440	32.19 ± 0.063	168	32.05 ± 0.119
Leukocyte count	135	9,906 ± 277	393	9,706 ± 156	116	10,552 ± 299
Neutrophils	133	53.82 ± 0.840	390	55.52 ± 0.490	115	54.03 ± 0.961
Lymphocytes	133	26.55 ± 0.603	390	28.30 ± 0.389	115	29.01 ± 0.844
Monocytes	133	6.42 ± 0.213	390	6.30 ± 0.119	115	6.41 ± 0.228
Eosinophils	133	13.07 ± 0.782	390	10.02 ± 0.360	115	9.97 ± 0.689
Plasma protein value	169	7.66 ± 0.051	518	7.63 ± 0.023	186	7.71 ± 0.039
Reticulocyte count	27	0.857 ± 0.097	64	0.975 ± 0.058	29	0.981 ± 0.109

TABLE 8.—*Relation Between Distance from Hypocenter and Hematologic Findings: Comparison of Mean Difference Between Established Pairs According to Distance*

	Distance from Hypocenter					
	0 to 1 Km.		1 to 2 Km.		Over 2 Km.	
Observation	No.	Mean Difference and Standard Error	No.	Mean Difference and Standard Error	No.	Mean Difference and Standard Error
Erythrocyte count	93	+212,000 ± 65,000	256	+17,000 ± 33,000	88	−3,000 ± 65,000
Hemoglobin concentration	92	+0.64 ± 0.154	264	+0.92 ± 0.100	90	+ 0.48 ± 0.146
Mean cell hemoglobin	92	−0.20 ± 0.305	250	+0.44 ± 0.152	88	+ 0.97 ± 0.299
Leukocyte count	91	− 489 ± 417	277	+ 323 ± 214	88	− 852 ± 357
Neutrophils	83	−0.02 ± 1.427	266	−0.59 ± 0.834	84	− 1.05 ± 1.32
Lymphocytes	83	+3.05 ± 1.070	266	+1.23 ± 0.640	84	+ 1.86 ± 0.990
Monocytes	83	+0.09 ± 0.314	266	−0.00 ± 0.180	84	+ 0.20 ± 0.349
Eosinophils	83	−2.11 ± 1.178	266	−0.48 ± 0.573	84	− 1.00 ± 0.988
Plasma protein value	92	−0.10 ± 0.063	264	+0.04 ± 0.036	90	− 0.12 ± 0.057

ever, the two studies are not entirely comparable. In order to analyze the possibility that those subjects who received the most radiation contributed disproportionately to the observed differences in the two series, the data have been broken down in three different ways. In tables 7 and 8, the data are presented in terms of the subject's distance from the hypocenter of the explosion, with individual subjects classified as to whether they were within 1 kilometer, between 1 and 2 kilometers, or beyond 2 kilometers at the time of the explosion. No attempt has been made in this analysis to evaluate further the shielding factor. In tables

9 and 10, the data are presented in terms of the extent of scalp epilation reported by the subject; three grades of epilation were established, corresponding to loss of under one third of the hair, loss of between one third and two thirds, and loss of over two thirds. Finally, in tables 11 and 12, the data have been analyzed according to the reported symptomatologic severity of the radiation sickness, as

TABLE 9.—*Relation Between Extent of Epilation and Hematologic Findings: Comparison of Mean Values*

Observation	Subjects with Grade 1 Epilation * No.	Mean and Standard Error	Subjects with Grade 2 Epilation No.	Mean and Standard Error	Subjects with Grade 3 Epilation No.	Mean and Standard Error
Erythrocyte count	296	4,542,000 ± 28,000	116	4,607,000 ± 45,000	200	4,464,000 ± 37,000
Hemoglobin concentration	432	12.77 ± 0.064	159	13.06 ± 0.105	266	12.79 ± 0.092
Hematocrit reading	383	40.87 ± 0.191	135	41.43 ± 0.310	223	40.94 ± 0.268
Mean cell volume	265	88.14 ± 0.443	102	88.24 ± 0.714	164	88.34 ± 0.605
Mean cell hemoglobin	295	28.43 ± 0.142	120	28.63 ± 0.224	200	28.56 ± 0.200
Mean cell hemoglobin concentration	382	32.07 ± 0.0.2	135	32.32 ± 0.122	223	32.35 ± 0.106
Leukocyte count	300	10,046 ± 202	120	9,836 ± 242	202	9,550 ± 211
Neutrophils	300	54.52 ± 0.60	120	55.98 ± 0.82	200	54.61 ± 0.73
Lymphocytes	300	28.80 ± 0.46	120	27.31 ± 0.69	200	27.16 ± 0.53
Monocytes	300	6.42 ± 0.14	120	5.98 ± 0.20	200	6.53 ± 0.17
Eosinophils	300	10.24 ± 0.41	120	10.79 ± 0.76	200	11.69 ± 0.64
Plasma protein value	432	7.64 ± 0.025	159	7.68 ± 0.042	266	7.66 ± 0.037
Reticulocyte count	54	0.968 ± 0.066	29	0.902 ± 0.081	35	0.930 ± 0.068

* In this and the subsequent table, grade 1 epilation indicates loss of under one third of the hair; grade 2, loss of between one third and two thirds, and grade 3, loss of over two thirds.

TABLE 10.—*Relation Between Extent of Epilation and Hematologic Findings: Comparison of Mean Difference Between Established Pairs*

Observation	Subjects with Grade 1 Epilation No.	Mean Difference and Standard Error	Subjects with Grade 2 Epilation No.	Mean Difference and Standard Error	Subjects with Grade 3 Epilation No.	Mean Difference and Standard Error
Erythrocyte count	205	+37,000 ± 42,000	83	+25,000 ± 64,000	142	**+107,000 ± 50,000**
Hemoglobin concentration	209	**+0.22 ± 0.110**	86	+0.10 ± 0.166	143	**+0.44 ± 0.135**
Mean cell hemoglobin	204	+0.19 ± 0.189	82	+0.26 ± 0.290	141	+0.15 ± 0.242
Leukocyte count	221	+ 120 ± 256	87	— 548 ± 375	140	+ 21 ± 304
Neutrophils	203	—0.29 ± 0.974	87	—2.18 ± 1.373	134	+0.15 ± 1.072
Lymphocytes	203	+0.95 ± 0.714	87	**+2.66 ± 1.175**	134	**+2.56 ± 0.823**
Monocytes	203	+0.19 ± 0.214	87	+0.52 ± 0.281	134	**—0.55 ± 0.255**
Eosinophils	203	—0.55 ± 0.652	87	—0.79 ± 1.155	134	—1.40 ± 0.876
Plasma protein value	209	—0.04 ± 0.038	86	—0.05 ± 0.070	143	+0.02 ± 0.051

judged by the cocurrence of nausea, anorexia, malaise, vomiting, gingivitis, diarrhea, pharyngitis, petechiae and purpura. Grade 1 includes those persons with nausea and/or anorexia; grade 2, those with vomiting and/or malaise, with or without the symptoms of grade 1; grade 3, those with gingivitis and/or diarrhea, with or without the symptoms of grades 1 or 2, and grade 4, those with pharingitis, petechiae and/or purpura, with or without the signs and symptoms of grades 1, 2 or 3. In all three analyses (tables 7 through 12) available data for

a few individual subjects, not readily classifiable, have been omitted. This is admittedly a rough classification at the best, but it probably is as satisfactory as possible under the circumstances. A statistical analysis revealed, as might have

TABLE 11.—*Relation Between Severity of Radiation Sickness and Hematologic Findings: Comparison of Mean Values*

Observation	Subjects with Grade 1 Radiation Sickness * No.	Mean and Standard Error	Subjects with Grade 2 Radiation Sickness No.	Mean and Standard Error	Subjects with Grade 3 Radiation Sickness No.	Mean and Standard Error	Subjects with Grade 4 Radiation Sickness No.	Mean and Standard Error
Erythrocyte count	43	4,556,000 ± 61,000	87	4,578,000 ± 48,000	201	4,592,000 ± 33,000	290	4,460,000 ± 31,000
Hemoglobin concentration	97	12.42 ± 0.110	137	12.87 ± 0.098	260	12.90 ± 0.079	358	12.90 ± 0.077
Hematocrit reading	90	39.06 ± 0.350	127	40.96 ± 0.307	209	41.20 ± 0.268	313	41.44 ± 0.219
Mean cell volume	39	86.59 ± 1.06	86	87.91 ± 0.65	175	87.11 ± 0.52	246	89.70 ± 0.49
Mean cell hemoglobin	43	27.76 ± 0.338	94	28.32 ± 0.262	200	28.11 ± 0.174	291	29.03 ± 0.157
Mean cell hemoglobin concentration	86	31.72 ± 0.152	127	32.08 ± 0.109	209	31.62 ± 0.093	313	32.36 ± 0.101
Leukocyte count	45	10,811 ± 516	98	10,102 ± 317	210	9,795 ± 229	288	9,656 ± 170
Neutrophils	43	53.75 ± 1.09	97	54.11 ± 1.02	208	54.82 ± 0.65	278	55.56 ± 0.62
Lymphocytes	43	28.40 ± 1.15	97	28.90 ± 0.74	208	28.56 ± 0.54	278	27.04 ± 0.47
Monocytes	43	6.13 ± 0.28	97	6.44 ± 0.26	208	6.25 ± 0.17	278	6.42 ± 0.14
Eosinophils	43	11.99 ± 1.19	97	9.91 ± 0.80	208	9.29 ± 0.44	278	10.17 ± 0.47
Plasma protein value	97	7.54 ± 0.059	146	7.69 ± 0.04	260	7.65 ± 0.034	358	7.67 ± 0.029
Reticulocyte count	8	1.175 ± 0.122	21	1.236 ± 0.113	32	0.844 ± 0.088	55	0.879 ± 0.055

* In this and the subsequent table, grade 1 sickness indicates nausea and/or anorexia; grade 2, vomiting and/or malaise, with or without the symptoms of grade 1; grade 3, gingivitis and/or diarrhea, with or without the symptoms of grades 1 or 2, and grade 4, pharyngitis, petechiae and/or purpura, with or without the symptoms of grade 1, 2 or 3.

TABLE 12.—*The Relation Between Severity of Radiation Sickness and Hematological Findings: Comparison of Mean Differences Between Established Pairs*

Observation	Subjects with Grade 1 Radiation Sickness No.	Mean Difference and Standard Error	Subjects with Grade 2 Radiation Sickness No.	Mean Difference and Standard Error	Subjects with Grade 3 Radiation Sickness No.	Mean Difference and Standard Error	Subjects with Grade 4 Radiation Sickness No.	Mean Difference and Standard Error
Erythrocyte count	25	+25,000 ± 110,000	68	+25,000 ± 62,000	128	−11,000 ± 46,000	218	**+110,000 ± 43,000**
Hemoglobin concentration	26	+0.36 ± 0.242	68	**+0.01** ± 0.154	132	+0.22 ± 0.135	221	**+ 0.38 ± 0.113**
Mean cell hemoglobin	25	+0.46 ± 0.601	65	−0.22 ± 0.340	127	**+0.65 ± 0.235**	217	**−0.04** ± 0.183
Leukocyte count	34	+ 30 ± 718	72	− 218 ± 461	129	+ 120 ± 324	221	**− 106 ± 230**
Neutrophils	31	−1.74 ± 2.439	72	+1.28 ± 1.608	120	−0.35 ± 1.128	210	**−1.14 ± 0.920**
Lymphocytes	31	+3.26 ± 1.900	72	−0.79 ± 1.182	120	+1.47 ± 0.879	210	**+2.81 ± 0.703**
Monocytes	31	+0.60 ± 0.476	72	−0.21 ± 0.299	120	−0.06 ± 0.283	210	+0.07 ± 0.216
Eosinophils	31	−1.97 ± 1.606	72	+0.03 ± 1.331	120	−0.05 ± 0.829	210	−1.31 ± 0.669
Plasma protein value	26	−0.02 ± 0.112	68	−0.10 ± 0.076	132	+0.08 ± 0.050	221	−0.05 ± 0.039

been expected, a high degree of positive association between these criteria for estimating the relative amount of radiation.

From a study of tables 7 through 12, three observations of some possible significance emerge:

1. The erythrocyte count showed a uniform tendency, as indicated in all these tables, to be lower in the groups presumably receiving the most radiation, whether

judged by nearness to the hypocenter, by amount of epilation or by severity of radiation sickness. There were no unequivocal or clearcut parallel variations in the hemoglobin concentration or hematocrit reading, although minor variations were present.

2. By all three of the same standards, the depression of the lymphocyte count noted in table 2 appeared to be best defined for those who were most severely irradiated.

3. The elevation of the eosinophil count in irradiated persons, also brought out in table 2, likewise appeared best defined for the more heavily irradiated subjects (tables 7 through 10), although the data are not in complete agreement (tables 11 and 12). Whether this was a true effect of irradiation or merely reflected an increased incidence of parasitic infection in the heavily irradiated persons, due to lowered resistance and/or poorer food conditions, with increased infection at the time of the bombing, will be discussed further later in this report.

In the preceding section, it was noted that those subjects who had received the severest burns and trauma nevertheless appeared to show the highest erythrocyte counts. The results reported in this section would seem to indicate that those who received the greatest amount of irradiation had at the time of writing the lowest erythrocyte counts. One plausible hypothesis that would bring these two tendencies into a single pattern is that of those persons who were heavily irradiated and also received severe burns or other injuries many died. This would explain, among the epilated survivors who composed this series, a relative deficiency of those persons with both severe injuries and severe irradiation and a relative excess of those severely burned but not heavily irradiated, and/or those severely irradiated but without extensive burns or other injuries. It is felt that the present data are inadequate to serve as a basis for a rigorous test of this hypothesis.

COMMENT

It may safely be assumed that the majority of persons in this series reporting epilation in consequence of the atomic bombing exhibited within two months after the event a major depression in the number of formed elements of the peripheral blood.[1] The studies herein reported reveal that two years after the bombing the peripheral blood manifested almost complete recovery from this insult to the hemopoietic system. However, there did appear to be a number of slight residua at the time of the study, of no apparent clinical significance but of definite statistical validity. In this section we shall attempt an evaluation of the meaning of these findings. First, however, as basic to any adequate discussion, the question of comparability of the control and the epilated populations on all scores except the irradiation factor must be considered.

The atomic bombing at Hiroshima produced sudden, widespread chaos. Casualties mounted to the tens of thousands, and in spite of valiant attempts, adequate care of the survivors was almost completely lacking. There was complete interruption of all normal economy for

a period of many weeks, and relief supplies failed to meet the demand in many instances. On the other hand, although Kure, the site of control observations, was subjected to bombings over a period of several months, the casualties were relatively few in number. Although there undoubtedly occurred disorganization of the normal economy, the degree and duration were minor in comparison with Hiroshima. Thus, the people were not subjected to the extreme privations encountered in Hiroshima. In the ensuing discussion, one question must constantly be kept in mind: Are the differences in the hematologic values observed in the two groups actually a residual effect of ionizing irradiation, or are they related to the associated unhygienic and innutritious aftermath? Also, it must be recognized that the surviving irradiated group were, within themselves, a selected group of the total population irradiated.

Erythrocyte Count.—It was indicated in table 2 that the irradiated population of Hiroshima had a mean erythrocyte count slightly below that of the nonirradiated population of Kure, the difference amounting to 65,000 to 83,000 cells per cubic centimeter, or approximately 1.6 per cent of the Kure mean. There was a correspondingly slight reduction in hemoglobin concentration (the difference was 0.26 to 0.30 Gm. per hundred cubic centimeters, or about 2.1 per cent of the Kure mean) and in hematocrit reading (0.48 per cent; about 1.2 per cent of the Kure mean). Since there were no significant differences relating to the cell constants, these differences were attributed to variations in the numbers of comparable cells rather than to qualitative effects on the erythrocytes. The important reservation relating to the spread of the distribution in Hiroshima will be discussed later in the paper.

The effect of ionizing irradiation on erythropoiesis has received considerable attention. The information in the literature on the results of long-continued irradiation and that on effects of repeated small doses of radiation is not strictly applicable in the interpretation of the data of this study. The literature on the erythrocytic response to acute exposures deals almost exclusively with the early picture [28] and indicates

28. (*a*) Minot, G. R., and Spurling, R. G.: The Effect on the Blood of Irradiation, Especially Short Wave Length Roentgen-Ray Therapy, Am. J. M. Sc. **168**:215 (Aug.) 1924. (*b*) Shouse, S. S.; Warren, S. L., and Whipple, G. H.: Aplasia of Marrow and Fatal Intoxication in Dogs Produced by Roentgen Radiation of All Bones, J. Exper. Med. **53**:421 (March) 1931. (*c*) Lawrence, J. H., and Lawrence, E. O.: Biological Action of Neutron Rays, Proc. Nat. Acad. Sc. **22**:124 (Feb.) 1936. (*d*) Lawrence, J. H., and Tennant, R.: Comparative Effects of Neutrons and X-Rays on the Whole Body, J. Exper. Med. **66**:667 (Dec.) 1937. (*e*) Aebersold, P. C., and Lawrence, J. H.: The Physiological Effects of Neutron Rays, Am. Rev. Physiol. **4**:25, 1942. (*f*) Warren, S., and Dunlap, C. E.: Effects of Radiation on Normal Tissue: III. Effects

(Footnote continued on next page)

that there generally occurs a depression of erythropoiesis, with a resultant anemia within a few weeks, the severity of which is roughly related to the dose. The recovery from the anemia is relatively slow in comparison to the leukocytic recovery.[29] Stearner and others [28k] administered 600 r of whole body radiation to rats and then followed the peripheral hematologic picture for a total of one hundred and sixty days. The lowest values for hemoglobin concentration and erythrocyte count were observed on the eighteenth day and were followed with a sharp recovery period. However, on the average, recovery did not appear to be complete at any time within the one hundred and sixty day period, although with the statistical measures employed, the differences between irradiated and control animals were not significant beyond the ninety-fourth day. The work of Jacobson and others [28n, o] on the rabbit, although less conclusive statistically, tends to confirm the results of the work on the rat. Henshaw and others [30] observed relatively rapid recovery of the hematologic constituents in mice following single whole body exposures either to neutrons in doses up to 90 n or to gamma

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of Radiation on the Blood and the Hemopoietic Tissues, Including the Spleen, the Thymus and the Lymph Nodes, Arch. Path. **34**:562 (Sept.) 1942. (*g*) Beck, J. S. P., and Meissner, W. A.: Radiation Effects of the Atomic Bomb Among the Natives of Nagasaki, Kyushu, Am. J. Clin. Path. **16**:586 (Sept.) 1946. (*h*) Craver, B. N.: Radioactive Emanations: Their Nature, Mechanism of Action, Biological Effects, and Tolerance Limits, J. Indust. Hyg. & Toxicol. **29**:196 (May) 1947. (*i*) Cantril, S. T.; Jacobson, L., and Nickson, J. J.: The Effects of Irradiation on the Blood and Blood Forming Tissues, MDDC 991, January 1943; declassified May 1946. (*j*) Bloom, W., and Jacobson, L. O.: Some Hematologic Effects of Irradiation, Blood **3**:586 (May) 1948. (*k*) Stearner, S. P.; Simmons, E. L., and Jacobson, L. O.: The Effects of Total Body X Irradiation on the Peripheral Blood and Blood Forming Tissues of the Rat, MDDC 1319, U. S. A. E. C. (*l*) Suter, G. M.: Responses of Hematopoietic System to X-Rays, MDDC 824; declassified July 1947. (*m*) Howland, J. W., and Warren, S. L.: The Effects of Irradiation from the Atomic Bomb on the Japanese, MDDC 1301, U. S. A. E. C. (*n*) Jacobson, L. O., and Marks, E. K.: Comparative Action of Cyclotron Fast Neutrons and X-Ray: II. Hematological Effects Produced in the Rabbit by Fast Neutrons, MDDC 1372, U. S. A. E. C., June 1946; declassified Oct. 1947. (*o*) Jacobson, L. O.; Marks, E. K.; Simmons, E. L.; Hagen, C. W., and Zirkle, R. E.: Effects of X-Rays on Rabbits: II. The Hematological Effects of Total Body X Irradiation in the Rabbit, MDDC 1174, July 1946; declassified July 1947.

29. Warren and Dunlap.[28f] Cantril, Jacobson and Nickson.[28i] Bloom and Jacobson.[28j] Stearner, Simmons and Jacobson.[28k] Suter.[28l] Jacobson and Marks.[28n]

30. Henshaw, P. S., Snider, R. S.; Riley, E. F.; Stapleton, G. E., and Sinkle, R. E.: Comparative Late Effects of Single Doses of Fission Neutrons and of Gamma Rays, MDDC 1254, June 1946; declassified August 1947.

rays in doses up to 700 r; the only significant late hematologic finding noted was the development of lymphomas.

On the other hand, the Japanese diet had for at least the five years previous to the study been deficient in many respects, a factor which did not favor adequate blood formation.[27] From recent surveys, the composition of the average Japanese diet during that period can be estimated to have consisted of 60 Gm. of protein, 12 Gm. of fat and 400 Gm. of carbohydrate; however, only about one tenth of the protein intake was of animal origin.[7] It has been stated that meat eaters average a higher number of red cells than vegetarians.[31] Whipple and Robscheit-Robbins [32] have extensively investigated the effects of various nutrients on blood regeneration. Evidence indicates then, that diet is an extremely important consideration, and that in a population which originally had an inadequate base line standard, the further innutritious circumstances created by the atomic bombing could conceivably have resulted in such hematologic differences as are indicated here. Even the fact that erythrocyte values appeared to be most depressed in those persons who received the greatest amount of radiation may only indicate that these persons suffered the greatest material loss and so, economically, fared particularly badly, with consequent poor nutrition. The factors of irradiation and innutritious conditions perhaps were, in effect, additive.

Leukocyte Count.—There was found to be no significant difference between mean leukocyte counts for the irradiated and nonirradiated groups, but there was a slight depression of relative lymphocyte count, amounting to 1.39 to 2.02 per cent, and a slight elevation of relative eosinophil count, amounting to 0.99 to 1.83 per cent. The general increase in mean leukocyte count, in both epilated and control series, was probably an expression of the frequent infections observed, which were minor but which did not eliminate persons from the series.

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31. Wintrobe, M. M.: The Erythrocyte in Man, Medicine **10**:195 (May) 1930.

32. Whipple, G. H., and Robscheit-Robbins, G. S.: Blood Regeneration in Severe Anemia: Standard Basal Ration Bread and Experimental Methods, Am. J. Physiol. **72**:395 (May) 1925; Favorable Influence of Liver, Heart, and Skeletal Muscle in Diet, ibid. **72**:408 (May) 1925; Iron Reaction Favorable: Arsenic and Germanium Dioxide Almost Inert, ibid. **72**:419 (May) 1925; Green Vegetable Feeding, ibid. **72**:431 (May) 1925; Influence of Striated and Smooth Muscle Feeding, ibid. **79**:260 (Jan.) 1927; Influence of Kidney, Chicken and Fish Livers, and Whole Fish, ibid. **79**:271 (Jan.) 1927; Influence of Dairy Products on Hemoglobin Production, ibid. **79**:280 (Jan.) 1927. Whipple, G. H.: Hemoglobin Regeneration as Influenced by Diet and Other Factors, J. A. M. A. **104**:791 (March 9) 1935; Protein Production and Exchange in the Body Including Hemoglobin, Plasma Protein and Cell Protein, Am. J. M. Sc. **196**:609 (Nov.) 1938.

The extreme sensitivity of the lymphocyte to acute ionizing irradiation has been appreciated for many decades,[33] but recovery has been said to be adequate within a relatively short time.[28f] It has been recently reported, however, that in the rabbit, the lymphocyte count was depressed for a period of ninety days after acute exposure to 800 r.[28j] Other investigators have reported that in the case of rats exposed to large single doses of whole body radiation, a possible discernible effect was observable in the lymphopoietic tissue as long as thirty-five days later, even though recovery, as indicated by the state of the peripheral blood, was essentially complete at thirty days.[28k]

Our data do suggest that there possibly existed greater residual depression of the lymphocyte count in those persons who received the heavier doses of radiation, but likewise they may indicate that it was these groups which showed the greatest increase in percentage of eosinophils. Eosinophilia is of recognized occurrence during the recovery phase in acute exposure to ionizing irradiation in as much as 10 to 20 per cent of cases.[28a, f] However, for the most part, eosinophilia is related to chronic or repeated exposure.[34] The duration of eosinophilia following acute exposure has received little attention. The high incidence of parasitic infection undoubtedly accounts for the rather high values observed in the controls,[35] but whether the relatively higher values in the Hiroshima subjects were an expression of increased parasitic disease cannot be stated without further study. The unhygienic conditions so prevalent in Hiroshima for several months after the bombing certainly would have favored transmission and increased morbidity. If this was the causal relation, the depression of the lymphocyte count was perhaps only a compensatory depression, in view of the similar mean leukocyte counts. An increased incidence of parasitic infection in Hiroshima may, of course, be a partial explanation of the difference in erythrocyte counts.

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33. Minot and Spurling.[28a] Heineke, H.: Ueber die Einwirkung der Roentgenstrahlen auf Tiere, München. med. Wchnschr. **50**:2090, 1903.

34. Minot and Spurling.[28a] Martland, H. S.: Occupational Poisoning in Manufacture of Luminous Watch Dials: General Review of Hazard Caused by Ingestion of Luminous Paint, with Special Reference to the New Jersey Cases, J. A. M. A. **92**:466 (Feb. 9); 552 (Feb. 16) 1929; The Occurrence of Malignancy in Radioactive Persons, Am. J. Cancer **15**:2435 (Oct.) 1931.

35. (*a*) Duff.[6] (*b*) Weech, A. A.; Goettsch, E., and Reeves, E. B.: Nutritional Edema in the Dog: I. Development of Hypoproteinemia on a Diet Deficient in Protein, J. Exper. Med. **61**:299 (March) 1935.

Plasma Protein Values.—The plasma protein values in Hiroshima were slightly elevated over those in Kure. Whether this was on a basis of nutrition or of irradiation cannot be decided at the present time. To the extent that plasma protein levels could be taken as a criterion for gross malnutrition,[35b] there was no evidence of the possible greater impairment of nutrition in Hiroshima discussed previously. The high levels of plasma protein observed in both cities are noteworthy. Similar high levels were observed by the Joint Commission, using the copper sulfate method, in 1945.[1] The determination of plasma protein values by the copper sulfate gravity method depended on certain constants, derived from a study of American subjects. The necessary studies to determine whether the extrapolation to Japanese subjects was a valid procedure have not been carried out at the time of writing. It is possible that the character of the Japanese diet was reflected in the constituents of the blood to the point where a given value for specific gravity did not have the same significance for the two groups.[27]

Variation.—Perhaps one of the more significant statistical findings to emerge from this study is the greater variability of individual hematologic values in the irradiated group in comparison with those of the control group. In the case of determinations concerned with the erythroid elements, this greater variability seems to be due chiefly to the fact that counts for a certain fraction of the population, for reasons not entirely evident, had failed to return to normal levels, with a resultant increased spread in the distribution of individual determinations. That considerable qualitative and quantitative variability of hematologic recovery after irradiation exists within various animal species is a well recognized fact.[36] For leukocyte determinations in which the mean total counts are similar, the explanation is more obscure.

The fact that the standard deviations recorded for the control population are considerably greater than those commonly accepted may lead some to question the validity of conclusions concerning relative variability. Throughout this investigation, we have been particularly conscious of procedural errors. We have attempted to evaluate the limitations of the various hematologic methods by as precise an estimation as possible of the errors involved in the determination of each value. These attempts have indicated that there was a substantial error due to inherent deficiencies of the methods, and also to personal inter-

36. Warren and Dunlap.[28f] Bloom and Jacobson.[28j] Stearner, Simmons and Jacobson.[28k]

pretations of the "end point." The reflection of these errors in the values for cell constants has been pointed out in some detail. On the basis of certain statistical considerations, the expected ranges of the constants for 95 per cent of values have been found to be considerably larger than those generally accepted as describing the range of normal values. For instance, Wintrobe [16] stated that 98 per cent of normal determinations of mean cell volume would fall within ± 8.0 cubic microns of the mean, 87.0 cubic microns. Ninety-eight per cent of the frequencies represent ± 2.7 standard deviations; therefore, 1 standard deviation is $\frac{\pm 8.0}{2.7}$, or approximately ± 3.0 cubic microns. We have indicated, on the basis of calculations utilizing certain estimates of the variability of the hematocrit reading and the erythrocyte count and their correlation coefficient, that the standard deviation of the mean cell volume should approximate at least ± 5.2 cubic microns. The range for 98 per cent of values would then be $2.7 \times (\pm 5.2)$, or ± 14.0 cubic microns. But even if one accepts the fact that the values customarily accepted as representing the range of the constants are too narrow, it must be admitted that in the control samples of both Japanese and American subjects, the observed variation in the mean cell volume was significantly greater than the calculated expectation. At least three factors which may have contributed to the greater variability of this and other determinations can be recognized: (1) In calculating the statistical expectation, extremely conservative estimates of population variability were utilized; (2) this study involved a decidedly more heterogeneous control population than was the case in the studies of Americans, designed to determine the normal range of the blood constants, and (3) noncertified equipment was used. The further possibility of technicians' errors must be recognized. But whereas all these factors may have contributed to a greater real and apparent variability in the "normal" population used in this study than in other normal populations, they cannot be utilized to explain the differences between Kure and Hiroshima, since the two laboratories were operated under comparable conditions, with the same staff.

SUMMARY

An attempt has been made to answer the following question: What was the peripheral hematologic picture twenty to thirty-three months after the atomic bombing of Hiroshima, in persons who received relatively large amounts of whole body radiation?

The criterion adopted for the selection of relatively heavily irradiated subjects was the occurrence of scalp epilation. Epilated subjects were selected at random, through the use of a questionnaire. The majority were school children.

A control population comparable in age, sex, nutritional status and occupation was studied in the city of Kure, which is located some 18 miles (28.97 kilometers) from Hiroshima.

In Hiroshima, 924 subjects were examined; in Kure, 935.

Each person selected for study completed a brief history and was given a brief physical examination; as many of the following blood values as circumstances permitted were then determined: erythrocyte and leukocyte counts, differential blood count, hemoglobin concentration, hematocrit reading, plasma protein level and, for a smaller number of persons, reticulocyte count.

A detailed evaluation of the errors involved in the standard blood studies is presented, as a basis for an appreciation of the significance of these findings.

Results are compared not only in terms of the mean values for the two populations but also in terms of the mean differences between randomly established pairs of similar control and epilated individual subjects.

The irradiated subjects of this study appeared for the most part to have made a complete recovery from the depression of the peripheral blood values which may be assumed to have followed the bombing. However, various significant differences between the two populations were observed:

1. Erythrocyte count, hemoglobin concentration and hematocrit reading were slightly, but significantly, depressed for the subjects in Hiroshima.

2. Although the total leukocyte count was the same in the two cities, in Hiroshima there were a slight relative depression of lymphocytes and a slight elevation of eosinophils.

3. Plasma protein values were possibly slightly higher in Hiroshima.

4. There was significantly greater variability in the observations made in Hiroshima than in those made in Kure.

These differences cannot be attributed to a differential response on the part of any particular age or sex group.

Epilated persons who experienced associated flash burns or trauma showed mean erythrocyte values which were higher, if anything, than the values for those who did not suffer such associated injury, from

which it is inferred that the greater frequency of these injuries in Hiroshima than in Kure does not account for the hematologic differences between the groups.

Those individual subjects who, by any of a number of criteria, absorbed greater amounts of radiation tended to show the most pronounced depression in erythrocyte and lymphocyte counts and the greatest elevation in eosinophil counts.

It is felt that in view of the great medical and civil disruption in Hiroshima after the bombing, caution must be exercised in attributing the slight recorded differences to the atomic bombing, although it seems possible that irradiation was, to some extent, responsible.

CLINICAL SIGNIFICANCE OF BACTEROIDES

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AND
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SAN FRANCISCO

CERTAIN anaerobic, nonsporing, gram-negative bacilli are classified in the genus Bacteroides.[1] (Excluded from this designation are the genera Dialister and Fusiformis, the former being characterized by small size and the latter by pointed ends.) These organisms are saprophytic inhabitants of the intestine, the urinary tract, the pharynx and the female genital tract.[2] Comparatively few studies of infections induced by Bacteroides have been reported in this country. The impression prevails, therefore, that it is a rare, even exotic, cause of human disease. This report is concerned with the clinical importance of Bacteroides in a group of cases in which this organism was recovered.

Dack's comprehensive survey[3] may be consulted for a review of the morphology, taxonomy, biochemical reactions and antigenic characteristics of Bacteroides. "Bergey's Manual of Determinative Bacteriology"[1] presents a detailed, but provisional, classification of this group of bacteria. A number of provocative studies purporting to demonstrate the evolution of variant L type colonies from Bacteroides have been reported by Dienes and his collaborators.[4]

METHODS

The routine technics of anaerobic cultivation used in our laboratory were adequate for the isolation of Bacteroides. An anaerobe jar, such as that described by Brewer,[5] was utilized. Employment of a catalyst was found to be superfluous when a high degree of suction could be attained

From the Department of Medicine, Stanford University School of Medicine.

1. Breed, R. S., and others: Bergey's Manual of Determinative Bacteriology, ed. 6, Baltimore, Williams & Wilkins Company, 1948.

2. Lemierre, A.: On Certain Clinical Forms of Septicemia with "Funduliformis" Bacillus, in Hamburger, J.: Recherches médicales en France pendant la guerre 1939-1945, Paris, Ernest Flammarion, 1947, p. 7.

3. Dack, G. M.: Non-Sporeforming Anerobic Bacteria of Medical Importance, Bact. Rev. **4**:227, 1940.

4. (*a*) Dienes, L., and Smith, W. E.: The Significance of Pleomorphism in Bacteroides Strain, J. Bact. **48**:125, 1944. (*b*) Dienes, L.: The Isolation of L Type Cultures from Bacteroides with the Aid of Penicillin and Their Reversion into the Usual Bacilli, ibid. **56**:445, 1948.

5. Brewer, J. H.: A Modification of the Brown Anaerobe Jar, J. Lab. & Clin. Med. **24**:1190, 1939.

and when carbon dioxide and hydrogen were pumped into the jar in succession after the evacuation of air. None of the anaerobic methods of blood culture [6] were utilized. Routine methods of blood culture, suitable for the isolation of most aerobic and anaerobic bacteria, were used.

No attempt to identify individual species was made in this laboratory. The classification of Bacteroides has been simplified in recent years; at

TABLE 1.—*Sites from Which Bacteroides Was Isolated in 47 Cases*

Source	Number of Cases	Total Number of Cases
Blood	..	2
Cerebrospinal fluid	..	1
Thyroid gland	..	1
Abdomen	..	3
Intra-abdominal abscess	1	..
Retropertioneal abscess	1	..
Rectal abscess (carcinoma)	1	..
Lungs	..	5
Empyema	2	..
Lung abscess	1	..
Bronchiectasis	1	..
Postpneumonectomy bronchial fistula	1	..
Osteomyelitis	..	2
Otolaryngologic area	..	2
Maxillary sinus (right)	1	..
Auditory canal (right)	1	..
Urinary tract	..	4
Superficial lesions	..	12
Scalp abscesses	1	..
Deltoid abscess (left)	1	..
Hidradenitis suppurativa	1	..
Pararectal abscess	2	..
Inguinal abscess	2	..
Breast abscess	1	..
Sebaceous cyst abscess above right ear	1	..
Inflammation of parotid gland	1	..
Abscess of pilonidal cyst	1	..
Pyodermic ulcer of leg	1	..
Female genital tract	..	8
Tubo-ovarian abscess	3	..
Cul-de-sac abscess	1	..
Bartholinian abscess	1	..
Paraurethral abscess	1	..
Vaginal abscess	1	..
Vulval ulcer	1	..
Uterine culture	..	7
Totals	30	47

present, Bacteroides funduliformis and Bacteroides fragilis appear to be the principal species clinically recognized. The former is distinguished from the latter by its pleomorphism and its supposedly greater invasiveness.[6] However, the differences in the clinical manifestations of infection with the two species are relatively minor.[7] Dienes [4b] stated that any classification was unnecessary, implying that diversities in strains account for the assumed distinctions in species.

6. (*a*) Smith, W. E., and Ropes, M. W.: Bacteroides Infections, New England J. Med. **232**:31, 1945. (*b*) Pham, H. C.: Les septicémies dues au Bacillus funduliformis, Thesis, Paris, 1935.

7. Ternois: Les septicémies à Bacillus fragilis, Ann. de méd. **44**:201, 1938.

INCIDENCE

Bacteroides was recovered in the cases of 47 patients admitted to the Stanford University Hospital clinics in the eight year period from 1940 to 1948. The incidence of Bacteroides according to the source and the age and sex of the patients is compiled in tables 1, 2 and 3. Bacteroides, according to the data in table 1, is a ubiquitous organism. The female genital tract and various superficial areas of the body were the most common sources. Bacteroides was encountered most frequently in the cases of young adults, although all age groups were well represented. Infections of females were predominant in this series even when the female genital tract was excluded as a source.

TABLE 2.—*Incidence of Bacteroides According to Age of Patients*

Age, Years	Number of Patients	Percentage
1 to 15	6	12.8
16 to 30	19	40.4
31 to 45	12	25.5
46 to 60	6	12.8
61 and over	4	8.5
Totals	47	100.0

TABLE 3.—*Incidence of Bacteroides According to Sex of Patients*

	Male Patients		Female Patients	
	Number	Percentage	Number	Percentage
Incidence in all cases	14	30.0	33	70.0
Incidence in all cases excluding infections of genital tract	14	42.4	19	57.6

CLINICAL FINDINGS

Bacteremias.—The primary foci of Bacteroides septicemia and bacteremia include tonsillar and peritonsillar abscesses, similar lesions of the mouth and jaw, otitis media, purulent endometritis, infection of the urinary tract and intestinal abscesses.[8] Many of the reported Bacteroides septicemias might more accurately be designated as sepsis with bacteremia. These septicemias and bacteremias are usually morbid processes with a high mortality rate.[9] Arthritis, icterus, pulmonary emboli and

8. Lemierre, A.: (*a*)[2]; (*b*) On Certain Septicæmias Due to Anaerobic Organisms, Lancet **1**:701, 1936.

9. (*a*) Pham.[6b] (*b*) Lemierre, A.; Reilly, J., and Laporte, A.: Les septico-pyohémies à Bacillus funduliformis, Ann. de méd. **44**:165, 1938.

thrombophlebitis are common events.[10] Reid and others [11] concluded that local thrombophlebitis was the most characteristic finding in invasion of the blood stream by Bacteroides.

Case 1.—A Negro widow of 67 (chart 1) entered the Stanford University Hospitals on Dec. 20, 1945. A stricture of the bowel, probably the result of lymphogranuloma venereum, had necessitated the establishment of a colostomy in 1924. Diarrhea, which ceased in response to the administration of camphorated

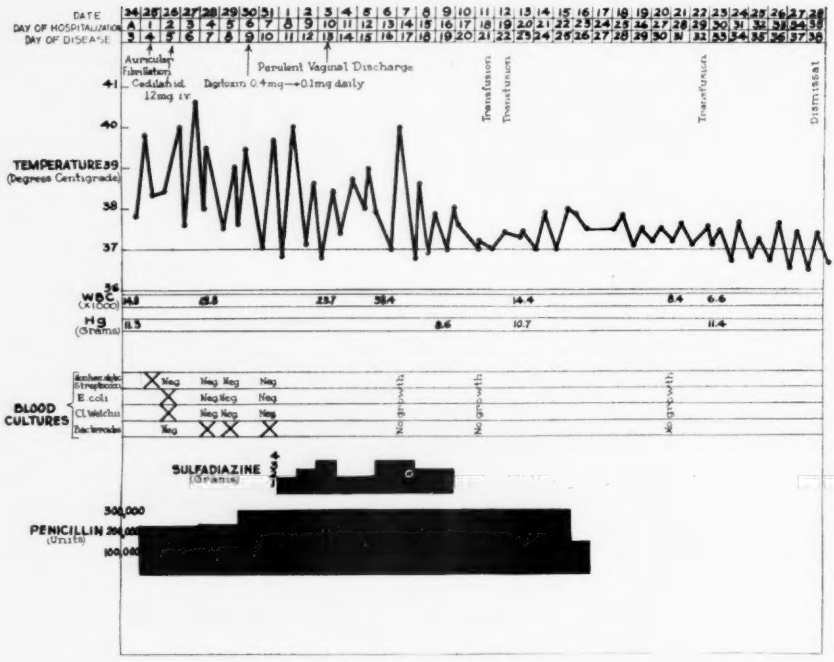

Chart 1.—Course in bacteremia (case 1). Cedilanid® is lanatoside C.

opium tincture (paregoric), had developed two days before her admission to the clinic. When she was first seen, a rectal stricture and a slight hemorrhage from the lower colostomy opening were noted. One day later, a headache, backache

10. Lemierre.[8b] Donzelot, E.; Meyer, A., and Olivier, J.: Deux nouvelles observations de septi cémie à "Bacillus funduliformis" (forme ictérique et forme suraiguë), Bull. et mém. Soc. méd. d. hôp. de Paris **52**:743, 1936.

11. Reid, J. D.; Snider, G. E.; Toone, E. C., and Howe, J. S.: Anaerobic Septicemia: Report of Six Cases with Clinical, Bacteriologic, and Pathologic Studies, Am. J. M. Sc. **209**:296, 1945.

and chill occurred. Three days afterward, on December 24, the patient was admitted to the hospital. While the patient was being examined late that day, a deep stupor developed precipitously.

The temperature was 37.8 C. (100.0 F.), the pulse rate 110, the respiration rate 30 and the blood pressure 130 systolic and 80 diastolic. Rales were heard over the right lung field and at the base of the left lung. Slight cardiac enlargement but no murmurs or arrhythmias were noted. There was a massive ventral hernia, and generalized pelvic tenderness was present.

The white blood cell count was 14,800 per cubic millimeter of blood. There was a marked predominance of neutrophils, nonfilamentous forms being very numerous. The hemoglobin concentration was 11.3 Gm. per cubic centimeter of blood. Slight proteinuria was noted. Elevated blood urea values (61 and 56.8 mg. per cent) were recorded early in the course. The icterus index, tests repeated twice, was 7.5. The plasma protein level was 7.5 Gm. per hundred cubic centimeters.

A nonhemolytic streptococcus was isolated from blood obtained one day after entry. This organism was inhibited with 0.1 unit of penicillin per cubic centimeter of blood. One day later, gram-negative bacilli of the paracolon group and Clostridium welchii were observed in the bloodstream. The latter was inhibited with 0.1 unit of penicillin per cubic centimeter. Bacteroides was the lone organism recovered from the blood on three successive occasions; it was resistant to 0.4 unit of penicillin per cubic centimeter. These positive blood cultures were made on the fourth, fifth and seventh days of hospitalization. Two subsequent blood cultures gave negative results. Coliform bacilli were isolated from the urine on the fifth day of hospitalization.

Atrial fibrillation developed one day after the patient was admitted. Immediate digitalization was followed by a reversion to sinus rhythm in two days. Maintenance doses of digitoxin were continued. Three hundred and twenty thousand units of penicillin were administered daily. Sulfadiazine (2 to 4 Gm. daily) was given, starting on the eighth day of hospitalization. Transfusions of whole blood and parenteral hydration constituted supportive therapy.

The spontaneous drainage of sanguinous, purulent material from the vagina occurred ten days after admission. A rectovaginal fistula originating from an abscess located in the distal end of the bowel was revealed to be the basis of the discharge.

On the tenth and eleventh days of hospitalization, certain of the organisms previously found in the blood stream, including aerobic gram-negative bacilli, Cl. welchii and Bacteroides, were isolated from the vaginal discharge. Coliform bacilli and penicillin-resistant nonhemolytic streptococci (organisms not previously recovered from the blood) were also obtained from the vaginal discharge.

The principal diagnoses were rectal fistula due to lymphogranuloma venereum, pelvic abscess, rectovaginal fistula, bacteremia, arteriosclerotic heart disease and bronchopneumonia.

An extremely febrile course, including recurrent chills and severe prostration, persisted for two weeks. The temperature fluctuated greatly, reaching a height of 40.6 C. (105.1 F.) on one occasion.

The leukocytosis persisted for about three weeks, the count attaining a height of 38,400 about two weeks after the patient's entry. Anemia developed, the hemoglobin concentration falling to 8.6 Gm. and the red blood cell count to 2,800,000 by the sixteenth day of hospitalization. Improvement commenced shortly afterward, and the trend was one of progress despite recurrent chills and

fever, signs of pulmonary edema, transient dependent edema, an episode of nondescript precordial pain and hypertension. The patient was dismissed thirty-five days after her entry.

Bacteroides was the predominant, although not the initial, invader of the blood stream. The resistance of the organism to penicillin was reflected in the delayed response to therapy. It was apparent that the abscess of the bowel and the resultant rectovaginal fistula constituted the primary source of the bacteremia. Thrombophlebitis, arthritis and icterus, commonly present in invasion of the

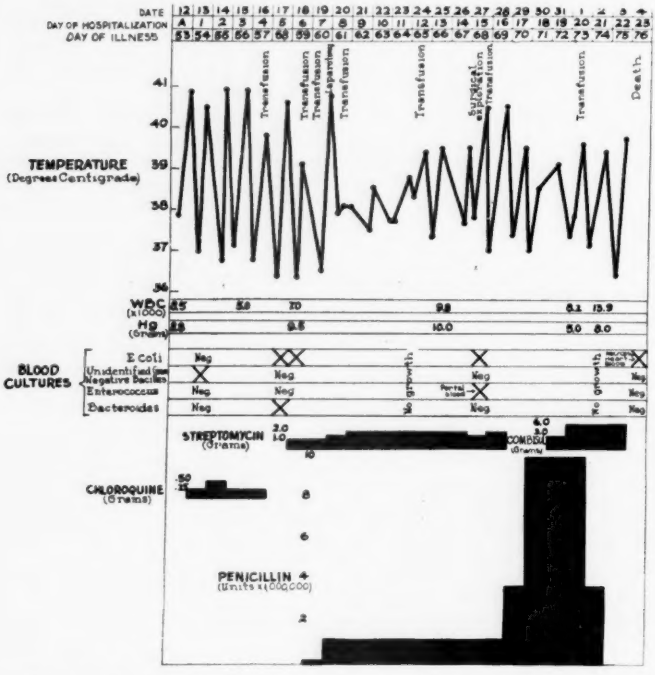

Chart 2.—Course in bacteremia (case 2). Combisul® contains equal parts of sulfadiazine, sulfathiazole and sulfamerazine.

blood stream by Bacteroides, were conspicuously absent from this case. The frequent resemblance of Bacteroides sepsis with bacteremia to that caused by other pyogenic organisms has been stressed.[12]

Case 2.—A white housewife of 39 (chart 2) had been in good health until March 21, 1948, when colicky lower abdominal pain, nausea, vomiting and diarrhea began, followed in two days by temperatures to 104 F. Chills and fever

12. Teissier, P.; Reilly, J.; Rivalier, E., and Stéfanesco, V.: Les septicémies primitives dues au Bacillus funduliformis, Ann. de méd. **30**:97, 1931.

recurred daily, but the abdominal distress subsided after the third week of illness. About 1,000,000 units of penicillin had been administered without effect just prior to the patient's entry to the Stanford University Hospital on May 12.

The temperature was 37.8 C (100.0 F.); the pulse rate was 100, and the blood pressure was 120 systolic and 75 diastolic. The patient was sallow and listless. A soft, systolic murmur along the left sternal border, tenderness in the right upper quadrant of the abdomen and a palpable spleen extending 4 finger-breadths below the left costal margin were the only contributory observations at that time.

A leukocyte count of 18,600 had supposedly been observed nine days prior to entry. On admission, the white blood cell count was 8,640 with 79 per cent neutrophils. Pronounced anemia was present at the time of entry and became intensified, despite blood transfusions, with a decline to a hemoglobin concentration of 5.0 Gm. and a red blood cell count of 1,960,000 two days before the patient's death. The corrected sedimentation rate on entry was 67 mm. per hour. Early in the course, the direct bilirubin value was 1.4 mg. per hundred cubic centimeters and the indirect bilirubin value, 3.2 mg.; the reaction for urinary urobilinogen was positive in a dilution of 1:160, and the icterus index was elevated to 20. The icterus index subsequently declined, a value of 7.5 being recorded four days prior to the patient's death.

A variety of organisms were found in the blood, including a pigment-forming gram-negative bacillus, Bacteroides, Escherichia coli and, from the portal blood, enterococci. On the 3 occasions that Esch. coli were recovered prior to the patient's death, 5 to 10 micrograms of streptomycin per cubic centimeter were sufficient for complete inhibition. Conversely, the single specimen of Bacteroides isolated early in the course of the illness was resistant to 50 micrograms of streptomycin per cubic centimeter and to 6 units of penicillin per cubic centimeter. (Cultures made at autopsy of the appendical abscess and of heart blood revealed Esch. coli resistant to 60 micrograms of streptomycin per cubic centimeter.)

The fever, chills and lethargy continued. A progressive increase in the extent of splenic enlargement was noted. A laparotomy performed on the seventh day of hospitalization and a right posterior flank approach on the fifteenth day revealed no disease. Nineteen grams of streptomycin and 40,000,000 units of penicillin were administered within two weeks without effect. Chloroquine, given early for suspected malaria, digitalis and more than 20 Gm. of sulfonamide drugs were similarly ineffectual.

Signs of fluid at the bases of both lungs had developed by the twelfth day. Roentgenographic studies at that time revealed a frank pleural effusion on the right side. Pronounced dependent edema appeared on the fifteenth day of hospitalization but diminished in four days. The tachycardia increased, the rate rising to 130; there was a pronounced gallop rhythm. Protein, coarsely granular casts and white blood cells were observed in the urine fifteen days after admission. Meanwhile, swinging of the temperature, severe shaking chills and lethargy continued. The peritoneal fluid, cultured about one week prior to the patient's death, revealed numerous enterococci plus a few Esch. coli and a few hemolytic streptococci. A culture of the wound performed one day later showed a heavy growth of Esch. coli. Severe respiratory distress supervened twenty-three days after entry, and the patient died. A definite diagnosis was not made before death.

An autopsy revealed acute purulent appendicitis, acute purulent pyelophlebitis, multiple hepatic abscesses and chronic local peritonitis. It is believed that a

localized abscess formed at the site of the appendical adhesion to the pelvic portion of the peritoneum. Acute purulent involvement of the portal vein followed with ensuing multiple abscesses of the liver.

It is evident that Esch. coli was the principal cause of the septic process. The importance of the subordinate role performed by Bacteroides is difficult to evaluate. At a period when blood-borne Esch. coli were definitely sensitive to streptomycin, the single culture of Bacteroides was refractory to the antibiotic therapy then in progress. It should be noted further that a heavy growth of Esch. coli may readily mask the presence of Bacteroides, particularly inasmuch as an obligate anaerobic bacterium is considerably more fastidious about its environmental requisites than is Esch. coli. Bacteroides has been described as a frequent cause of appendicitis.[13] Hepatic abscesses and bacteremias have been known to arise from Bacteroides appendicitis.[14]

Meningitis.—Smith and his associates,[15] in 1944, reviewed 14 cases of Bacteroides infection of the central nervous system, 4 of them being their own. Meningitis was diagnosed in 12 instances. Chronic otitis media was the common origin of such infection, and invasion of the mastoid was rather common. Bacteroides meningitis was characterized by the acute onset of fever, headache, and stiffness of the neck. The spinal fluid has been found to be cloudy, with an elevated cell count, increased protein content and decreased sugar content. The prognosis was hopeless prior to the advent of chemotherapy and proper supportive therapy. Three of the 4 patients whose cases were described by Smith and others and a patient in another recent case of Bacteroides meningitis [16] recovered from the disease. Sulfonamide therapy and proper surgical and supportive therapy were important factors in the cases with a favorable outcome.

Case 3.—A Negro of 21 (chart 3) had had a mass located at the angle of the jaw on the right side since the age of 2. The mass had enlarged despite surgical excision and radiation therapy. Roentgenograms made in October had revealed chronic, bilateral mastoiditis. The patient entered the hospital on December 14, 1947; diagnoses of mixed tumor and, later, adenocarcinoma of the parotid gland were made.

The area around the right ear was extremely firm, the right ear protruded, the right external auditory canal was occluded by blood and pus and sound was lateralized to the right in the Weber test. The mouth could be opened only 2 cm. Paralysis of the right facial nerve was present.

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13. Veillon, A., and Zuber, A.: (*a*) Sur quelques microbes strictement anaérobies et leur rôle dans la pathologie humaine, Compt. rend. Soc. de biol. **4**:253, 1897; (*b*) Recherches sur quelques microbes strictement anaérobies et leur rôle en pathologie, Arch. de méd. expér. et d'anat. path. **10**:517, 1898.

14. Lemierre.[8b] Lemierre, A., and Reilly, J.: Rôles des microbes anaérobies dans l'étiologie des septico-pyohémies consécutives aux appendicites, Presse méd. **53**:105, 1945.

15. Smith, W. D.; McCall, R. E., and Blake, T. J.: Bacteroides Infections of the Central Nervous System, Ann. Int. Med. **20**:920, 1944.

16. Ballenger, J. J.; Schall, L. A., and Smith, W. E.: Bacteroides Meningitis: Report of a Case with Recovery, Ann. Otol., Rhin. & Laryng. **52**:895, 1943.

Radical dissection of the right ear and the surrounding tissue was performed four days after the patient's entry. A hard, 10 by 5 cm. mass was found to be attached to tissue behind the right ear. This was excised, as was much of the ramus of the mandible and the first inch of the zygomatic process. A cerebrospinal leak occurred at the base of the skull during the operation. The patient's recovery from the operations was complicated by a severe hemorrhage and fever. Penicillin and streptomycin were administered and the right common carotid artery and internal jugular vein were ligated and divided on Jan. 1, 1948. A skin graft

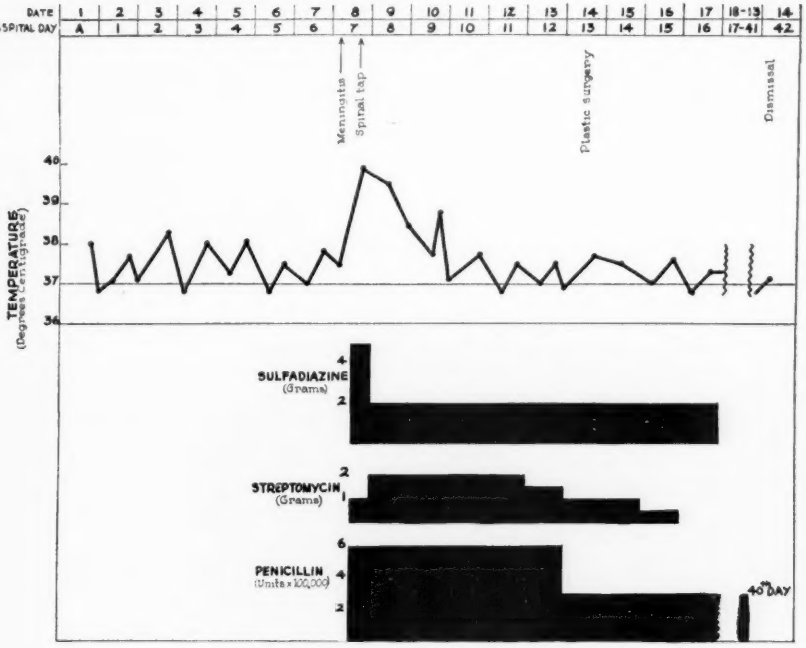

Chart 3.—Course in meningitis (case 3).

was applied on January 14. The white blood cell count was 11,150 on January 16.

The patient reentered the hospital on February 1 because of an infection involving the area from which skin had been obtained on the right posterior thigh. Drowsiness, irrationality, frontal headache and a temperature of 39.8 C. (103.6 F.) suddenly developed eight days later. Tenderness, pain and stiffness of the neck were present. A lumbar puncture revealed a high protein content and the presence of large numbers of polymorphonuclear leukocytes and of Bacteroides in pure culture in the spinal fluid. The white blood cell count was 8,920; the hemoglobin concentration was 12.5 Gm., and the red blood cell count was 4,400,000. Penicillin, streptomycin and sulfadiazine were promptly administered.

There was no nuchal stiffness or tenderness by the following day, and the temperature had declined to 38.5 C. (101.3 F.). Recovery was so rapid that another skin graft was undertaken on February 14. The patient left the hospital on March 14. There were no complaints or evidence of recurrence, either of meningitis or of the neoplasm, on November 16.

The sudden onset of fever, headache, irrationality and stiffness of the neck, and equally rapid recovery (probably in response to the simultaneous administration of sulfadiazine, streptomycin and penicillin) characterized this case of Bacteroides meningitis. The relative efficacy of the three therapeutic agents is difficult to evaluate. A successful outcome in other cases has been attributed, in part at least, to sulfonamide therapy. However, the extremely rapid response of this patient to treatment indicates only that one or the other of the antibiotic drugs, and possibly both, contributed to the favorable result.

The evidence of otitic infection on the entry of the patient and the history of mastoiditis diagnosed by roentgenographic examination provided a suitable background for the probable origin of the disease. One may surmise that the preceding major operation on the area of the right ear and the attendant stormy course were important contributory factors in the pathogenesis of the meningitis.

Involvement of the Thyroid Gland.—There has been casual mention of thyroiditis occurring in the course of Bacteroides septicemia.[8]

Case 4.—One patient in the series, a white man of 64, harbored Bacteroides in the thyroid gland. Moderate enlargement of the thyroid gland had been present for twenty to twenty-five years. The patient entered the hospital because sudden enlargement and tenderness of the thyroid gland associated with dysphagia had occurred four days before. Fever, mild leukocytosis and moderate anemia were present. The mass in the neck, weighing 308 Gm., was removed by a subtotal thyroidectomy; the temperature then rapidly declined to normal. The patient was discharged thirty-four days after entry. The surgical and pathologic reports concurred in a diagnosis of thyroid adenomas plus hemorrhages, both old and recent, into the thyroid gland and thyroiditis. A microscopic examination disclosed areas of leukocytic infiltration and necrosis.

Sanguinous material aspirated from the enlarged thyroid gland thirteen days after the patient's entry revealed Bacteroides in pure culture. Similar organisms were recovered from the thyroid gland at the time of the operation nine days later. Three blood cultures, taken on the tenth, thirteenth and fourteenth days of hospitalization, respectively, were sterile.

It is believed that this is the first report in the United States of the isolation of Bacteroides from the thyroid gland.

Abdominal Lesions.—Bacteroides has been found in cases of appendicitis,[13] peritonitis [6a] and infected carcinoma of the large intestine.[17] Only 1 of 5 patients with Bacteroides peritonitis without bacteremia died, whereas 5 of 6 instances of Bacteroides septicemia arising from infection in carcinoma of the bowel were fatal. Smith and Ropes [6a] pointed

17. Dixon, C. F., and Deuterman, J. L.: Postoperative Bacteroides Infection: Report of Six Cases, J. A. M. A. **108**:181 (Jan. 16) 1937.

out the probable frequency of intra-abdominal infections due to Bacteroides; leakage of the contents of the bowel was the postulated route of invasion.

Case 5.—A white man of 28 (chart 4) had had pain in the right lower quadrant of the abdomen, diagnosed as due to appendicitis, about six weeks prior to his entry to the hospital. An appendectomy had been performed, and there was apparent recovery within eleven days. The first attack of pain in the right upper quadrant occurred about two weeks later. This quickly subsided but was

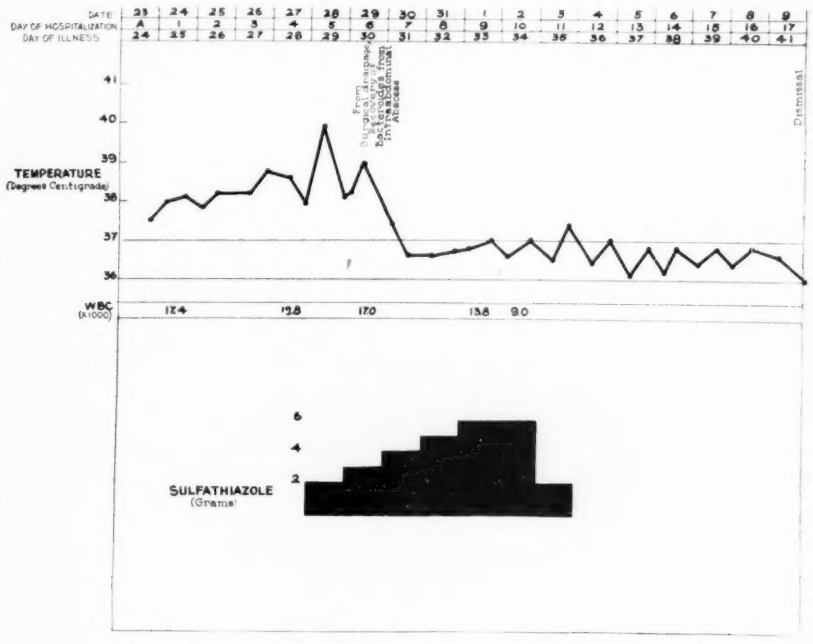

Chart 4.—Course in case 5 (intra-abdominal abscess).

followed in a week by a severe exacerbation of similar pain plus a temperature of 101 F., nausea and vomiting, and possible blood in the stools. After four days, the attack subsided. On the patient's entry, aside from a temperature of 37.7 C. (99.9 F.), the only contributory findings were tenderness and spasm in the right upper quadrant.

The white blood cell count varied between 15,000 and 18,000 and returned to normal after surgical intervention. The icterus index and the value for the van den Bergh test were within normal limits. Bacteroides was isolated in pure culture from material obtained from the intra-abdominal abscess at the operation.

Roentgen studies, performed one day after admission, were inconclusive aside from failure to visualize the gallbladder. The fever and tenderness of the right upper quadrant persisted until the sixth day of hospitalization. At that time, a laparotomy revealed an intra-abdominal abscess, which was immediately incised and drained. Omental adhesions were observed on the lateral and posterior surfaces of the gallbladder, the extrusion of 2 or 3 ounces (57 to 85 Gm.) of thick, yellow pus occurring on digital probing of the involved area. The liver was normal in appearance. Despite considerable foul, serous drainage, the subsequent course was characterized by rapid improvement and the patient was dismissed from the hospital seventeen days after admission.

It may be significant that appendicitis preceded the occurrence of the intra-abdominal abscess in case 5. Bacteroides, the lone etiologic agent discovered in this instance, has been described as an appendical inhabitant.[13] The relatively benign course in this case corresponded with the usual favorable outcome of Bacteroides peritonitis.[6a]

Bacteroides was recovered from abscesses secondary to malignant neoplasms in 2 additional cases:

Case 6.—A woman of 22 had a retroperitoneal sarcoma. Bacteroides and Bacillus subtilis were present in a large abscess adjacent to the neoplasm. The Bacteroides was penicillin sensitive. The patient's early death did not seem related to the abscess, the highly malignant sarcoma accounting for the rapid downhill course.

Case 7.—Bacteroides and anaerobic nonhemolytic streptococci were recovered from an abscess adjacent to an inoperable rectal carcinoma. The absence of severe symptoms, aside from a rectal hemorrhage readily ascribed to the neoplasm, indicated that the abscess was not of great clinical importance.

Osteomyelitis.—Proven Bacteroides osteomyelitis, occurring in the head of the right femur, was reported by Chandler and Breaks.[18] This infection, appearing in the case of a 12 year old white boy, probably originated from acute otitis media due to Bacteroides. The course was stormy and prolonged, leukocytosis and anemia persisting throughout the acute phase. Sequestrectomy was required to eradicate the lesion.

Case 8.—A 5 year old white boy was admitted to the Stanford University Hospitals on Aug. 13, 1945. A mandibular mass had been present for one year. Some enlargement of the swelling had been noted for the three months previous to admission but had become particularly obvious four days before as the result of a fall on the involved area.

On entry, the temperature was 37.6 S (99.7 F.). The sole contributory finding was a hard, bony, nontender mass, 2 cm. in diameter, on the left anterior aspect of the mandible. Neither leukocytosis nor anemia were observed during the course except at one period, in February 1948, when a white blood cell count of 18,800 and a hemoglobin concentration of 10.5 Gm. were recorded.

18. Chandler, F. A., and Breaks, V. M.: Osteomyelitis of the Femoral Neck and Head Caused by Bacterium Necrophorum (Bacillus Funduliformis), J. A.M. A. **116**:2390 (May 24) 1941.

Roentgenograms confirmed the clinical impression of a bony tumor, and surgical excision of an osteoma was performed three days after entry. Persistent low grade fever, prolonged drainage of the wound and separation of the wound edges complicated recovery, but the response to penicillin was good. However, a fracture at the surgical site was observed within four months after the patient's dismissal. A chronic course of recurrent suppurative complications, requiring repeated surgical intervention and intensive chemotherapy, followed for over two years.

The patient reentered the hospital in July 1946 because of the breakdown of an old surgical incision. This lesion originated from a small pustule in the area. An infected bone graft was diagnosed. Purulent discharge and low grade fever persisted for nearly three months. The removal of sequestrums and the administration of over 5,000,000 units of penicillin were required before the infection subsided.

Two successive specimens of purulent drainage from the infected mandible, obtained on July 3 and July 6, revealed a large number of Bacteroides plus a moderate number of coagulase-positive Staphylococcus aureus and nonhemolytic streptococci. The staphylococcus was inhibited with 0.05 unit of penicillin per cubic centimeter; the streptococcus was sensitive to 0.1 unit of penicillin per cubic centimeter, and the Bacteroides was resistant to 0.1 unit of penicillin per cubic centimeter, the highest concentration of the antibiotic drug employed. A culture of material from a superficial abscess of the jaw on June 26, 1947, revealed a light growth of nonhemolytic streptococci. This organism was inhibited with 0.1 unit of penicillin per cubic centimeter.

Superficial purulent drainage complicated surgical intervention as recently as February 1948, but two cultures of material from the wound, made in March, were sterile and the status of the patient at the time of this report is quite satisfactory.

In this case, the correlation between the delayed response to penicillin therapy and the resistance in vitro of Bacteroides to the antibiotic drug is of interest. Furthermore, Bacteroides, isolated twice from the infected bone graft, was the predominant organism at that time. A sequestrectomy was required in this instance as in Chandler and Break's case.

CASE 9.—A white man of 45 entered the hospital on March 8, 1941, because of nuchal pain and limitation of motion to the right for approximately three months. By the date of entry, a swelling on the right side of the neck, a sore throat, fever, chills and a slight obstruction to breathing had developed. A tender, nonfluctuant, indurated mass, 2 cm. in diameter, was located on the right side on the neck.

Radiation therapy, surgical aspiration, immobilization of the neck and the administration of sulfonamide drugs induced no clearcut improvement. A biopsy of the mass on the ninth day after admission revealed stony-hard, avascular, gray-white, poorly circumscribed inflammatory tissue. Draining cervical sinuses appeared about one month after entry. A slight gain in weight and subjective improvement were noted during a three month interval in the hospital. The disease progressed after the patient's transfer to another institution, and cervical osteomyelitis was diagnosed. Death occurred eight months after the onset. Bronchopneumonia secondary to the cervical osteomyelitis was the apparent cause.

A diagnosis of tuberculosis had been tentatively eliminated by a roentgenologic examination and by results of cultures and animal inoculation. No organisms were isolated from the drainage on surgical aspiration. Numerous pleomorphic

alpha hemolytic Bacteroides were recovered on May 23, 1941 from pus obtained from the draining cervical sinuses. A few coagulase-positive Staphylococcus aureus organisms accompanied the Bacteroides.

The history of sore throat, fever and chills at the time of entry indicates that the pharynx, a common primary focus of Bacteroides infection, may have been the source of infection in this patient, followed by metastatic osteomyelitis of the spine. Tenderness, edema and even suppuration of the lateral aspects of the neck have been observed during the development of postanginal Bacteroides septicemia.[8b]

Pulmonary Infections.—In 1904, Guillemot and others [19] reported the isolation of Bacteroides from purulent exudate in 11 of 13 cases

TABLE 4.—*Cases of Pulmonary Infection in Which Bacteroides Was Isolated*

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
10	45	F	W	Empyema	Thoracic pain, fever and signs of pleural effusion following esophageal perforation; sulfonamide drugs given throughout course; thoracotomy performed; 240,000 units penicillin given in 4 days after operation; death 3 weeks after entry.	Many Bacteroides and a few Staph. albus isolated from empyema at operation
11	46	M	W	Empyema	Fever, cough, sputum and thoracic pain (left) of 6 weeks' duration; good response to surgical drainage; penicillin given before entry and after operation; sulfonamide drugs given after operation; marked tendency to recurrent thrombophlebitis	Bacteroides sole organism recovered at time of rib resection; subsequent culture of empyema fluid revealed Bacteroides and nonhemolytic streptococci
12	43	M	W	Lung abscess	Severe cough, foul sputum and fever of 8 months' duration; treatment, including several major operative procedures and administration of much penicillin, of no definite benefit	Large numbers of Bacteroides accompanied by many anaerobic nonhemolytic streptococci and Actinomyces recovered from cavity of abscess on one occasion
13	43	M	W	Bronchiectasis	Severe illness marked by cough, foul sputum and extreme weakness of 10 months' duration; no response to heavy doses of penicillin, streptomycin and sulfadiazine; death immediately after pneumonectomy	Bacteroides plus anaerobic hemolytic and nonhemolytic streptococci and Actinomyces isolated from sputum
14	56	M	W	Postpneumonectomy bronchial fistula	Cough, night sweats and hemoptysis of 1 year's duration found to be caused by bronchogenic carcinoma; temporary improvement after pneumonectomy, but death within 9 months	Gas-producing Bacteroides present in postoperative pleural fluid in association with Staph. aureus (coagulase-positive)

of pulmonary infection (mainly putrid empyema). Later, Cohen [20] stated that pus recovered at operation yielded Bacteroides in 14 of 16 cases of abscess of the lung. Anaerobic diphtheroids and anaerobic nonhemolytic streptococci were found in all 16 specimens, aerobic bacteria being isolated in only 3 instances. It is of interest that suppurative pulmonary emboli have been reported to be a common occurrence in Bacteroides septicemias.[21] Other studies have indicated the importance of anaerobic organisms in the pathogenesis of pulmonary suppuration.

19. Guillemot, L.; Halle, J., and Rist, É.: Recherches bactériologiques et expérimentales sur les pleurésies putrides, Arch. de méd. expér. et d'anat. path. **16**:571, 1904.

20. Cohen, J.: The Bacteriology of Abscess of the Lungs and Methods for Its Study, Arch. Surg. **24**:171 (Feb.) 1932.

21. Lemierre.[2] Lemierre, Reilly and Laporte.[9b]

Bacteroides was recovered in 2 cases of empyema, 1 of an abscess of the lung, 1 of bronchiectasis and 1 of postpneumonectomy fistula in this study.

Case 10.—Empyema, occurring in the case of a white woman of 45, was of unusual interest inasmuch as it seemed to be secondary to esophageal perforation following instrumentation with a Plummer bag. The empyema was characterized by pain in the right side of the thorax, fever and signs of pleural effusion. A stormy course followed, and death occurred three weeks after the patient's entry. A variety of organisms, mainly nonhemolytic streptococci and Staphylococcus aureus, were recovered by aspiration, but Bacteroides was not isolated until a thoracotomy was performed: At that time, the fluid drained at operation contained an extremely heavy growth of Bacteroides and a few Staphylococcus albus. Sulfonamide drugs were given throughout the illness, and a total of 240,000 units of penicillin were administered during the four postoperative days. It may be more than a coincidence that Bacteroides were the final organism discovered prior to the patient's demise. Previous reports have commented on possible secondary fatal infection by Bacteroides in cases of debilitated patients.[17]

Case 11.—The other case of empyema, in a white man of 46, was characterized by the acute onset of fever, cough, the production of sputum and pain in the left side of the thorax. Penicillin was administered prior to the patient's entry. Bacteroides requiring 0.2 unit of penicillin per cubic centimeter for inhibition was isolated in pure culture from operative material obtained at the time of resection of a rib. Penicillin and sulfonamide drugs were administered after the operation. The subsequent culture of the drainage from the empyema cavity revealed Bacteroides and an anaerobic nonhemolytic streptococcus. This case contrasts with case 10, since a good result followed surgical intervention.

Other Cases.—Numerous other anaerobic organisms were recovered with Bacteroides from the lung abscess (case 12) and the site of the bronchiectasis (case 13). Operative material was the source of the organism in case 12. Intensive penicillin therapy was utilized in both cases, plus heavy doses of streptomycin and sulfadiazine in case 14. The recovery of Bacteroides did not coincide with the period of most intensive antibiotic therapy in either instance. The major organism recovered from the draining postpneumonectomy fistula (case 13) was a coagulase-positive Staphylococcus aureus, there being a sparse growth of Bacteroides. Bronchogenic carcinoma was the primary disease. In this instance, the Bacteroides as cultured was definitely a gas former, but gas was not noted in the patient's tissues. The formation of the fistula and the presence of Bacteroides may have been related. Shaw [22] observed the formation of a bronchial fistula following thoracotomy in a case of empyema, Bacteroides being recovered from the operative purulent material.

Otolaryngeal Lesions.—Bacteroides has been implicated as an important etiologic agent in chronic suppurative otitis media. A recent report [6a] mentioned its isolation in 2 such cases. Serious complications

22. Shaw, F. W., and Bigger, I. A.: Necrobacillosis of the Lung, J. A. M. A. **102**:688 (March 3) 1934.

ascribed to chronic purulent otitis media due to Bacteroides include generalized sepsis with bacteremia [2] and meningitis and brain abscess.[23]

This study contains reports of only 2 otolaryngeal cases:

CASE 15.—A woman of 45 had a severely inflamed right maxillary sinus which was discovered by antral puncture to contain pus from which Bacteroides was isolated in pure culture. Postnasal drip for five years, frontal headache for one and one-half years and the absence of relief after submucous resection marked the course prior to the patient's admission to the hospital. Considerable relief was gained by the puncture of the antrum.

CASE 16.—The other patient entered the clinic because of chronic otorrhea on the right side following a simple mastoidectomy one year before. Subsequently, postauricular swelling indicated a serious exacerbation of mastoiditis and radical mastoidectomy was performed. The drainage of thick, green pus from the mastoidectomy wound complicated recovery, but the response to local treatment was good. Bacteroides was isolated once from the right ear as the drainage from the wound was subsiding; Staphylococcus albus, diphtheroids and hemolytic streptococci were recovered concurrently (hemolytic streptococcus was the sole organism isolated from the right ear on two prior occasions). It seems reasonable to conclude that Bacteroides was a secondary invader.

Infections of the Urinary Tract.—Albarran and Cottet [24] reported the isolation of Bacteroides plus other anaerobic organisms and aerobic bacteria in 2 of 9 cases of pyelonephritis. Both cases were characterized by the presence of renal calculi. Two hundred grams of thick, fetid pus was obtained by ureteral catheterization in 1 of these cases. Also reported was the recovery of Bacteroides from 11 of 25 "urinary abscesses," perineal and periureteral infections being the main foci.

Bacteroides was isolated from the urine in 4 cases in this series. The organism was recovered in large numbers in 2 of these:

CASE 17—A woman of 24 experienced low grade fever, commencing one day after a normal delivery. This persisted, and tenderness over the breasts, the saphenous veins and the thighs developed two days later. A few white blood cells and marked bacteriuria were noted coincidentally with the beginning of fever. Pyelitis and possible thrombophlebitis were diagnosed. The patient received 8 Gm. of sulfathiazole in one week and recovered. The single culture of the urine, performed four days after the onset of the illness and four days after the institution of sulfonamide therapy, revealed numerous Bacteroides and a few nonhemolytic streptococci.

CASE 18.—The remaining case of heavy growth of Bacteroides in the urinary tract was that of a woman of 59, who had a history of renal infection on the right side and renal calculi of five years' duration. Other physicians had performed numerous diagnostic procedures and had given her repeated courses of sulfonamide drugs and penicillin. The most recent examination prior to admission had revealed the delayed appearance of dye from the right kidney and pyuria. Tenderness

23. Smith, McCall and Blake.[15] Ballenger, Schall and Smith.[16]

24. Albarran, J., and Cottet, J.: Des infections urinaires anaérobies, in Cong. internat. de méd. profess., de 1900, p. 281.

of the right costovertebral angle was elicited on the patient's entry. It was still present at the time of the second and final visit, eleven days later. Urinalysis revealed a slight trace of protein and 4 to 8 white blood cells per high dry field on entry. The only contributory finding eleven days later was 10 to 15 white blood cells per high dry field. An extremely heavy growth of Bacteroides in pure culture was recovered from the urine on entry and again eleven days later. The history of calculi may be significant since Albarran and Cottet[24] also observed them in both their cases of pyelonephritis with Bacteroides in the urine.

Other Cases.—The isolation of Bacteroides from the urine seemed to be of lesser significance in the other 2 cases. In case 19, in which the condition was diagnosed as a possible postpartum pyelonephritis, 400 Staphylococcus albus per cubic centimeter and a few Bacteroides were recovered from the urine at the same time that sulfonamide and penicillin therapy was instituted. In case 20, a few Bacteroides were present in the urine of the patient, who had no other evidence of infection of the urinary tract.

Cutaneous and Other Superficial Lesions.—Pustular eruptions of the skin have been observed in the course of bacteremic infection by Bacteroides.[2] A case of cutaneous abscesses of the hand acquired by a person in contact with an animal infected by Bacteroides has been described.[25] Little other concrete or detailed information about superficial Bacteroides infections is available.

Case 21.—A Negro aged 30 entered the hospital on July 18, 1946 with an eruption of the scalp of seven or eight months' duration. It commenced as a pruritic pimple which was first detected after the use of hot shot® hair dressing. A private physician prescribed a white salve, but it was without beneficial effect.

Fluctuant nodules and tumors were observed over the entire scalp with many areas of associated alopecia. Pus could readily be expressed from lesions in the right occipital region. Retroauricular and posterior cervical adenopathy were noted.

The laboratory data were noncontributory. No leukocytosis was noted.

A few coagulase-negative staphylococci (Staph. albus) were isolated from the draining lesions several times early in the course of the disease. The culture of material obtained by aspiration of an abscess about two months after the patient's entry revealed a heavy growth of Bacteroides plus a few anaerobic nonhemolytic streptococci and Staphylococcus albus. The culture of a similar lesion on November 17 revealed many gram-variable anaerobic organisms and a few albus organisms. The former were inhibited by 0.05 unit of penicillin per cubic centimeter and grew sparsely in 10 micrograms of streptomycin per cubic centimeter coincidentally with the period of penicillin therapy. The culture of purulent material on April 16, 1947 resulted in a moderately heavy growth of Bacteroides. The highest dilution of penicillin employed in this instance, 0.10 unit per cubic centimeter, had no inhibitory effect on Bacteroides. The last study, on October 2, again revealed Bacteroides. This very heavy growth was inhibited by 0.05 unit of penicillin per cubic centimeter.

25. Stemen, C. M., and Shaw, F. W.: Necrobacillosis of the Skin, J. Kansas M. Soc. **10**:405, 1910.

Sulfadiazine (1 Gm. every four hours for about three days) brought no improvement. Thereafter, numerous exacerbations of these relatively symptom-free lesions characterized the illness. All treatment, including surgical drainage and a regimen of 12,000,000 units of penicillin in oil and beeswax within thirty days, led to nothing more than quite temporary regression of the nodules and abscesses.

Bacteroides was probably the primary organism responsible for this unusual infection. Despite the absence of generalized toxicity, the condition was extraor-

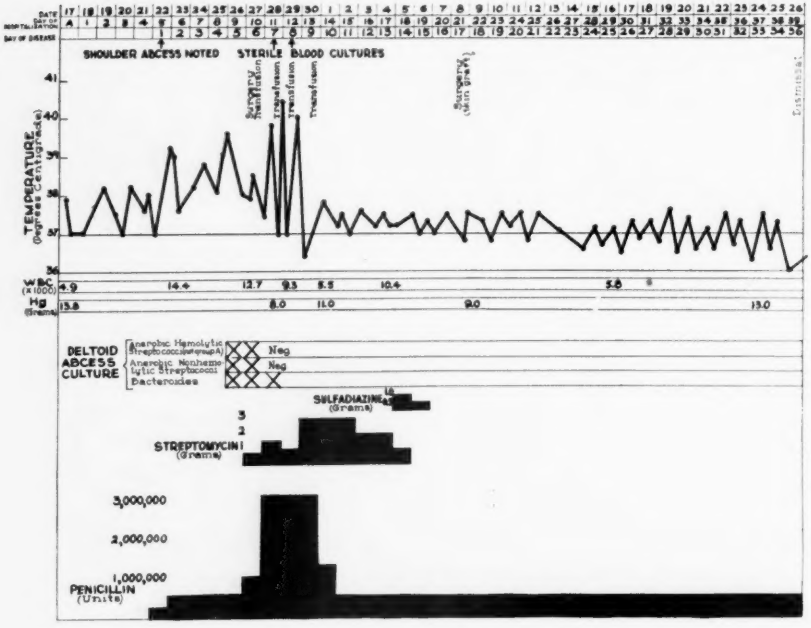

Chart 5.—Course in case 22 (abscess of the left deltoid muscle).

dinarily refractory to treatment. Neither repeated surgical drainage nor moderate amounts of penicillin seemed to have more than a transient beneficial effect.

Case 22.—Another severe infection was that of a white woman of 25 (chart 5) who had a deltoid abscess from which Bacteroides was isolated three times, once alone. About two weeks of intensive therapy was required to bring the infection under control. A total of nearly 30,000,000 units of penicillin and 17 Gm. of streptomycin were administered. Radical débridement was performed because the abscess possessed the clinical and roentgenologic attributes of gas gangrene at one stage of the illness. Gas gangrene antitoxin and 1.5 Gm. of sulfadiazine were also prescribed. Pronounced anemia persisted throughout the acute phase of the disease.

CASE 23.—A heavy growth of Bacteroides was recovered from the draining sinuses of a woman of 18 with suppurative hidradenitis of the axillas. Numerous coagulase-negative staphylococci (Staph. albus) albus and a few nonhemolytic streptococci were isolated concurrently. Boils of the axillas had been present for two years prior to the entry of the patient, but the response to therapy, including the administration of penicillin and hot soaks, had been poor. Severe facial acne accom-

TABLE 5.—*Cases of Cutaneous and Other Superficial Lesions in Which Bacteroides Was Isolated*

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
21	30	M	N	Scalp abscesses	Recurrent abscesses of scalp resistant to all treatment, including 12,000,000 units of penicillin within 1 month and repeated surgical drainage; case followed over 2 years	Bacteroides isolated on only 2 occasions
22	25	F	W	Left deltoid abscess	Patient showed poor control of diabetes on entry, with fever, painful left shoulder and hot, tender abscess; clinical and roentgen evidence of gas gangrene; operation and high dosage of antibiotic drugs brought slow recovery; severe anemia in acute stage	Bacteroides recovered on 3 separate occasions, the third in pure culture after administration of penicillin; Clostridium not present
23	18	F	W	Hidradenitis suppurativa	Boils of axillas and facial acne for 2 years; no response to parenteral administration of penicillin; temporary remission with irradiation and local penicillin therapy; but recurrence of infection of left axilla in 1 month; draining sinuses on entry	Heavy growth of Bacteroides and coagulase-negative Staph. albus, plus a few nonhemolytic streptococci from draining sinuses
24	2	F	W	Abscesses of right groin and thigh	Scant, milky, sanguinous material aspirated from abscesses; leukocytosis and anemia present; response to surgical drainage and penicillin therapy; death due to medulloblastoma	Culture revealed only Bacteroides in both lesions
25	42	F	W	Parotitis	Parotitis discovered in course of work-up for cause of abdominal pain, fever and nausea and vomiting in a case of diabetes; Esch. coli bacteremia and enterococcic bacteriuria major findings	Bacteroides isolated once concurrently with 3 other genera of bacteria
26	30	M	W	Left pararectal abscess	Abscess of 1 month's duration responded rapidly to surgical drainage; similar lesion noted 15 years earlier	Bacteroides and coagulase-negative Staph. albus only organisms observed
27	21	F	N	Left pararectal abscess	Deep vaginal tear following delivery with forceps; later, fever and anal pain; relief by incision and drainage	Bacteroides 1 of 3 organisms isolated
28	52	F	W	Breast abscess	Painful mass in left breast of 4 days' duration; good response to surgical drainage	Bacteroides and anaerobic nonhemolytic streptococci recovered
29	12	F	N	Abscess of sebaceous cyst superior to ear	Mass above right ear present for 1 year with recurrence and enlargement 2 weeks before entry; recession following incision and drainage	Bacteroides and nonhemolytic streptococci only organisms isolated
30	34	M	N	Left inguinal abscess	Gonorrhea treated with penicillin prior to onset of adenopathy; enlargement of left inguinal lymph node; rapid regression following aspiration	Bacteroides and anaerobic nonhemolytic streptococci recovered
31	22	F	W	Pilonidal cyst abscess	Tender abscess at base of sacrum present for 4 days; good response to surgical drainage	Heavy growth of Bacteroides; two other organisms in small numbers
32	61	M	W	Pyodermic ulcer of left leg	Pyodermic ulcer decreased in size and improved in appearance within 10 days after administration of penicillin, débridement and local therapy	Heavy growth of Bacteroides, coagulase-negative Staph. aureus, hemolytic streptococci and Cl. welchii

panied the onset of the hidradenitis and persisted. Two million seven hundred thousand units of penicillin administered at this hospital were of no avail. However, local radiation therapy and 3,600,000 units of penicillin injected directly into the axillas brought marked improvement. This regimen was continued after the patient's discharge from the hospital, but severe infection of the left axilla nevertheless recurred about one month later. This report parallels a description of a case of suppurative hidradenitis of nineteen years' duration, reported by Smith and Ropes,[6a] from which Bacteroides was repeatedly isolated in mixed culture with

staphylococci or streptococci. In Smith and Rope's case, the buttocks, chest, back and face had also been involved at various stages of the disease.

CASE 24.—Abscesses of the groin and thigh in the case of a child of 2 demonstrated a delay in response to surgical drainage and the administration of penicillin. The infection was of minor importance in comparison with the fatal medulloblastoma in this case. The pus expressed from the lesions was of a scanty, milky, sanguinous appearance rather than being of the bulky, foul, gray-green variety usually described in abscesses due to Bacteroides.

CASE 25.—Although few in number, the Bacteroides discovered in this case of parotitis may have been of greater importance than a first glance at the data would indicate. The Bacteroides and anaerobic nonhemolytic streptococci, although quite sparse, were the most penicillin resistant of the flora. Antibiotic therapy and chemotherapy were begun following the isolation of Bacteroides; it was not recovered subsequently.

OTHER CASES.—The remainder of the conditions, including 2 pararectal abscesses (cases 26 and 27), an abscess of the breast (case 28), an abscess of the ear area (case 29), an abscess of an inguinal lymph node (case 30), an abscess of a pilonidal cyst (case 31) and a pyodermic ulcer of the leg (case 32), were relatively mild and responded well to simple surgical drainage, the administration of antibiotic drugs or local therapy. It is perhaps noteworthy that the patients in 2 of the 12 cases of superficial lesions (those of the severe deltoid abscess [case 22] and of the parotitis [case 25]) had diabetes.

Infection of the Female Genital Tract.—Bacteroides is a common saprophyte of the female genital tract.[26] It has been implicated mainly as a secondary invader in chronic and subacute pathologic processes of this system, but its importance in puerperal fever has been indicated.[26b] Severe and even fatal puerperal infection, particularly following deliveries complicated by operative intervention, has been attributed to Bacteroides.[27]

Bacteroides was the lone organism isolated in the present series from most of the circumscribed lesions of the female genital tract, accompanying bacteria being present in only 3 of the 7 cases described.

Three cases of tubo-ovarian abscess requiring surgical intervention were examples of serious invasion of the genital tract by Bacteroides.

CASE 33.—A white woman aged 21 had a history of a ruptured appendix one year previously with an apparently good response to surgical intervention. Chills, fever, lower abdominal pain and a mass in the right adnexa were noted two months prior to entry. Rest, the administration of sulfonamide drugs and the incision and drainage of the mass brought periods of remission, but exacerbations followed. A mass developed in the left fallopian tube, and, about five months after entry, a subtotal hysterectomy, a bilateral salpingectomy and a left oopherectomy were performed during a quiescent phase of the illness. Convalescence was uneventful.

26. (*a*) Lemierre.[2] (*b*) Burdon, K. L.: Bacterium Melaninogenicum from Normal and Pathologic Tissues, J. Infect. Dis. **42**:161, 1928.

27. Harris, J. W., and Brown, J. H.: Description of a New Organism That May Be a Factor in the Causation of Puerperal Infection, Bull. Johns Hopkins Hosp. **40**:203, 1927.

Leukocytosis and anemia were present throughout the acute course. A pure culture of Bacteroides was recovered from the tubo-ovarian abscess on the left side, discovered at operation. The possibility was entertained that the illness had actually been initiated by a retained portion of the ruptured appendix.

CASE 34.—The second example of tubo-ovarian abscess occurred in the case of a woman of 29 who entered the hospital with a history of vaginal hemorrhage, dysuria and lower abdominal pain for one week. Slight improvement had

TABLE 6.—*Cases of Circumscribed Lesions of the Female Genital Tract in Which Bacteroides Was Isolated*

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
33	21	F	W	Left tubo-ovarian abscess	Appendicitis and appendectomy 1 year before entry; chills, fever, pain and mass in right lower quadrant of abdomen for 2 months before; leukocytosis and anemia present; 74 Gm. of sulfonamide drugs given in 2 months; subtotal hysterectomy, bilateral salpingectomy and left oophorectomy 4 months after entry	Bacteroides recovered in pure culture from tubo-ovarian abscess discovered at operation
34	29	F	W	Right tubo-ovarian abscess	Lower abdominal pain, vaginal hemorrhage, dysuria and fever for 1 week; sulfonamide drugs given prior to entry; mass in cul-de-sac and, later, in right lower quadrant palpated; subtotal hysterectomy, bilateral salpingectomy and right oophorectomy performed 6 months after entry	Bacteroides recovered in pure cultures from abscess at operation
35	23	F	W	Tubo-ovarian abscess	Induced abortion about 4 months before entry; vaginal hemorrhage, lower abdominal pain and fever marked course; on entry, tenderness in lower abdomen and mass in right adnexa; penicillin and sulfadiazine no aid; excision of abscess and cornual portion of right tube	Bacteroides and anaerobic nonhemolytic streptococci isolated from tubo-ovarian abscess at time of operation
36	23	F	N	Cul-de-sac abscess	History of gonorrhea 1 year before entry; recurrent episodes of pain and tenderness in lower abdomen of 4 months' duration; mass in right adnexa on entry; 200,000 units penicillin given 6 days before isolation of Bacteroides; colpotomy of cul-de-sac abscess at that time (2 years after admission)	Bacteroides recovered in pure culture from abscess of cul-de-sac
37	46	F	W	Bartholinian abscess	Painless lump on vulva for 3 weeks prior to entry; persisted for next 7 months despite repeated surgical drainage; no antibiotic therapy or chemotherapy	Pure culture of Bacteroides recovered from bartholinian abscess
38	48	F	N	Right vulval ulcer	Small mass noted on right side of vulva 7 years before entry; ulcer developed which was resistant to therapy; intensive sulfonamide therapy prior to positive culture; painful swelling present on right side of vulva 25 years earlier	Bacteroides, Staph. aureus and nonhemolytic streptococci isolated from ulcer
39	17	F	W	Vaginal abscess	Vaginal discharge for 4 months; congenital stricture of vagina; 300 cc. pus drained surgically; relief after surgery; postoperative penicillin therapy	Bacteroides predominant organism; very few staphylococci and nonhemolytic streptococci recovered
40	52	F	W	Paraurethral abscess	Pain and burning on urination for 2 weeks; relief after surgical drainage; previous history of treated gonorrhea; sulfonamide drugs given at time of surgical procedure	A few Bacteroides only organisms isolated from paraurethral abscess

followed the administration of about 3 Gm. of sulfathiazole on the previous day. Fever and a mass in the cul-de-sac were the principal findings on admission. Rapid improvement followed with symptomatic therapy. Two and one-half months later, the patient reentered with an acute exacerbation of lower abdominal pain and with a mass in the right lower quadrant. Diathermy brought relief, but reentry with a similar episode occurred three months later and subtotal hysterectomy, bilateral salpingectomy and oophorectomy on the right were performed at this time. A tubo-ovarian mass and chronic inflammation were present on the right side. A pure culture of Bacteroides was isolated from the tubo-ovarian mass. The laboratory findings were noncontributory, aside from a single slightly elevated white blood cell count.

CASE 35.—The third example of tubo-ovarian abscess, in the case of a woman of 23, followed an induced abortion. A hemorrhage immediately followed instrumentation with a catheter, while fever and lower abdominal pain commenced ten days later; these symptoms continued until admission. Moderate tenderness in the lower part of the abdomen and a mass in the right adnexa were present. The temperature was 37.2 C. (99.0 F.) and remained normal although the patient reported that a temperature of 102 F. had been present prior to entry. The white blood cell count was 16,000 cells per cubic millimeter of blood. The pain persisted and the mass enlarged despite the administration of 1,650,000 units of penicillin within one week and of 8 Gm. of sulfadiazine within three days. Dilation and curettage and exploratory laparotomy were performed nine days after entry. A tubo-ovarian abscess was observed on the right side; this, plus the cornual portion of the fallopian tube, was excised. A week later, the patient was dismissed in good condition. Bacteroides and anaerobic nonhemolytic streptococci were isolated from the tubo-ovarian abscess.

The foregoing 3 cases simulated gonococcal salpingitis. They were reminiscent of a case of Bacteroides salpingitis and peritonitis (no. 6 in the series reported by Smith and Ropes [6a]).

CASE 36.—In this case of abscess of the cul-de-sac, the patient had a history of possible gonorrhea about one year prior to entry. Episodes of lower abdominal pain recurred, as did adnexal masses, during a two year period before the abscess was outlined. The illness, at the time of the appearance of the mass in the cul-de-sac, was associated with chills, fever and lower abdominal pain, all of which subsided after a posterior colpotomy. Approximately 1,000,000 units of penicillin in one week and sulfonamide in the customary dosage were administered in concert with the surgery. Bacteroides was the only organism recovered from the abscess. Bacteroides may have been a late invader, Neisseria gonorrhoeae being the likely pimary etiologic agent.

OTHER CASES.—Another history of gonorrhea, confirmed in this instance, preceded the onset of a paraurethral abscess (case 37). Sulfathiazole was administered concurrently with surgical drainage, but resolution of the lesion seemed to be due to the operation. The drug was given prior to the isolation of Bacteroides in a case of vulval ulcer (no. 38) and led to no marked improvement. Penicillin was prescribed after successful surgical drainage of the vaginal abscess in case 39. No antibiotic therapy or chemotherapy was administered to the patient with a bartholinian abscess (case 40); the lesion persisted for six months despite repeated aspiration.

Seven cases of infection of the uterine tract were characterized by the presence of Bacteroides in the uterine or vaginal discharge. Five of the 7 cases were examples of postpartum infection. In case 41, Bacteroides was penicillin resistant in contrast to the single other organism, a nonhemolytic streptococcus, which was penicillin sensitive. Penicillin and sulfonamide drugs, alone or in combination, were given in all 5 cases. Four patients improved rapidly, but recovery in case 42 was complicated by postpartum hemorrhage, anemia, cervicitis and endometritis. A long-standing vaginal discharge and a recent bout of vaginal hemorrhage characterized 1 nonparturient case (no. 43). The discharge gradually abated, the administration of diethylstilbestrol being of apparent aid. In the other nonparturient case (no. 44), the patient had a vaginal discharge of two weeks' duration which apparently subsided spontaneously. Only slight inflammation of the vagina had been noted at the time of admission.

Seven examples of probable saprophytic Bacteroides[26] within the female genital tract were observed in this study. The need for more active study of the role of Bacteroides in uterine infection, particularly in the "postpartum state," is evident.

TABLE 7.—*Cases in Which Bacteroides Was Isolated from Urine and Vaginal Discharge*

Case	Age	Sex	Race	Source	Clinical Characteristics	Bacteriologic Observations
41	19	F	W	Uterine discharge	Postpartum fever, tenderness of uterine fundus, costovertebral tenderness and foul lochia; improvement after administration of 240,000 units of penicillin in 1 day	Penicillin-resistant Bacteroides principal organism recovered; few penicillin-sensitive nonhemolytic streptococci also present
42	31	F	W	Uterine discharge	Patient febrile before and after delivery; hemorrhage and severe anemia immediately post partum; abdominal pain and vaginal discharge, due to subacute and cystic cervicitis, occurred 10 weeks post partum; no antibiotic therapy or chemotherapy	Bacteroides and anaerobic nonhemolytic streptococci isolated
43	65	F	N	Uterine discharge	Long-standing vaginal discharge and recent vaginal hemorrhage; cessation of discharge after diethylstilbestrol treatment. No antibiotic therapy or chemotherapy	Bacteroides and anaerobic nonhemolytic streptococci isolated
44	5	F	W	Vaginal discharge	Vaginal discharge for 2 weeks; only slight inflammation of vagina at time of entry; spontaneous remission without therapy	Heavy growth of Bacteroides, Staph. albus, nonhemolytic streptococcus and Cl. welchii
45	16	F	N	Uterine discharge	Fever and retention of membranes post partum; fever disappeared 2 days after start of sulfadiazine therapy (4 Gm. daily)	Pure culture of Bacteroides; blood culture negative
46	17	F	W	Uterine discharge	Postpartum fever and burning on urination; Esch. coli present in urine; good response to sulfonamide and penicillin therapy	Many Bacteroides and few Staph. albus isolated
47	29	F	W	Uterine discharge	Fever accompanied postpartum retention of membranes; temperature normal within 1 day of commencement of penicillin therapy	Bacteroides and anaerobic nonhemolytic streptococci isolated

TABLE 8.—*Organisms Isolated Coincidentally with Bacteroides*

Cases in which pure culture of Bacteroides was obtained		13
Cases in which mixed cultures were obtained		34
Anaerobic nonhemolytic streptococcus	16	
Nonhemolytic streptococcus	11	
Staph. albus	10	
Staph. aureus (coagulase-positive)	7	
Anaerobic hemolytic streptococcus	4	
Hemolytic streptococcus	3	
Coliform bacilli	3	
Diphtheroids	1	
Pneumococcus (type V)	1	
Pseudomonas aeruginosa	1	
Alcaligenes faecalis	1	
Actinomyces	1	
Coagulase-negative Staph. aureus	1	
Cl. welchii	2	

ACCOMPANYING FLORA

A brief survey of the organisms isolated concurrently with Bacteroides is presented in table 8. The high incidence of anaerobic streptococci, particularly of the nonhemolytic variety, seems to be more than fortuitous. Frequent association of anaerobic streptococci with

Bacteroides has been observed in other studies,[28] and the possibility of a symbiotic relationship between Bacteroides and anaerobic streptococci has been suggested.[29]

TREATMENT

The treatment of infection by Bacteroides has included administration of potassium iodide,[30] vigorous aeration of local lesions,[31] the administration of sulfonamide drugs,[32] streptomycin [33] and penicillin,[2] surgical drainage [34] and ligation of thrombosed veins, particularly of the internal jugular vein in septicemias.[9b] Definite value has been attributed to intensive treatment with sulfonamide drugs, particularly sulfapyridine; however, its beneficial effects have been noted to be irregular.[2] The importance of supportive therapy, particularly blood transfusions and the parenteral administration of fluids, has been emphasized.[16]

Surgical drainage was usually effective for the management of accessible localized lesions in cases of this study. There were exceptions, of which examples were case 21 (scalp abscesses) and case 40 (repeatedly occurring bartholinian abscess).

In a recent review of septicemias due to Bacteroides funduliformis, Lemierre [2] claimed the administration of penicillin to be a most efficacious means of combating this infection, having observed a remarkable therapeutic effect in several critical cases. Varying degrees of refractoriness to penicillin therapy were displayed in the present series. Bacteremia (case 1) and recurrent abscesses of the scalp (case 21) were not benefited by prolonged courses of penicillin. A compilation of penicillin sensitivities in vitro is interesting when correlated with clinical effects (see table 9).

Unfortunately, many of the sensitivity studies were not carried out beyond a concentration of 0.10 unit of penicillin per cubic centimeter. Furthermore, a number of specimens were not tested because of technical difficulties in culturing Bacteroides. It is clear, nevertheless, that the organism may be resistant to penicillin since 7 of 9 organisms tested displayed some degree of refractoriness to this antibiotic drug. Our

28. Lemierre, Reilly and Laporte.[9b] Cohen.[20]

29. Cohen.[20] Norris, C.: Suppurative Pyelophlebitis Associated with Anaerobic Micro-Organisms, J. M. Research **6**:97, 1901.

30. Shaw, F.: Human Necrobacillosis, Zentralbl. f. Bakt. **129**:132, 1933.

31. Martin, W. B.: Human Infection with B. Necrophorum, Am. J. Clin. Path. **10**:567, 1940.

32. Brown, A. E.; Williams, H. L., and Herrell, W. E.: Bacteroides Septicemia: Report of a Case with Recovery, J. A. M. A. **116**:402 (Feb. 1) 1941.

33. Cressy, N. L.; Lahey, W. J., and Kunkel, P.: Streptomycin in the Treatment of Bacterial Endocarditis, New England J. Med. **239**:497, 1948.

34. Smith and Ropes.[6a] Lemierre, Reilly and Laport.[9b]

data support Foley's demonstration [35] of the penicillin resistance of Bacteroides in vitro, 12 strains being uninhibited by 100 units of penicillin per cubic centimeter, and Dienes' observation [4b] that the L forms of Bacteroides are penicillin resistant. Clinical experience with the use of penicillin in Bacteroides infections is inadequate, but it is apparent that reliance on penicillin exclusively in such infections is not justifiable.

It has been claimed that streptomycin probably aided recovery in a case of Bacteroides endocarditis [33]; large doses of penicillin and sulfonamide drugs were given after streptomycin therapy was begun. However, the in vitro sensitivities of 12 strains of Bacteroides, ranging from 750 to 2,000 micrograms of streptomycin per cubic centimeter,

TABLE 9.—*Penicillin Sensitivity of Nine Strains of Bacteroides in Vitro*

Case	Source	Units Per Cc.	Comment
1	Blood	Resistant, 0.4	Patient febrile for 3 weeks; over 6,000,000 units penicillin administered
2	Blood	Resistant, 6	Esch. coli, predominant organism, streptomycin sensitive when Bacteroides resistant to 50 units streptomycin per cc.; death due to bacteremia and pylephlebitis despite administration of more than 40,000,000 units penicillin and 19 Gm. streptomycin
5	Retroperitoneal abscess	Sensitive, 0.05	Rapid downhill course with death due to the retroperitoneal sarcoma
7	Osteomyelitis of mandible	Resistant, 0.1	Response to surgical intervention and 5,000,000 units penicillin delayed
10	Empyema	Sensitive, 0.2; resistant, 0.1	Response to rib resection and tube drainage good
20	Abscesses of scalp	April 16, 1947: resistant, 0.1; October 2: sensitive, 0.05	Recurrent scalp abscesses present over 2 years; resistance to repeated surgical drainage and to 12,000,000 units penicillin administered in 1 month
29	Parotitis	Resistant, 0.1	Bacteroides not predominant organism
37	Uterine discharge	Resistant, 0.1	Bacteroides likely etiologic agent in postpartum uterine infection

indicated basic streptomycin resistance by this organism.[35] The value of the streptomycin used in the treatment of a few cases in the present study could not be determined. In case 2 (bacteremia), the single specimen of Bacteroides was resistant to 50 micrograms of streptomycin per cubic centimeter, and intensive streptomycin therapy did not prevent fatal termination. This agent may have played a role in the successful treatment of the deltoid abscess (case 22) and the meningitis (case 3).

COMMENT

In this series of cases of Bacteroides infection, the areas of predilection were the female genital tract and the superficial parts of the body. Bacteremia, meningitis, pulmonary infection, osteomyelitis, abdominal

35. Foley, G. E.: In Vitro Resistance of the Genus Bacteroides to Streptomycin, Science **106**:423, 1947.

abscesses, maxillary sinusitis and infections of the urinary tract were other varieties of Bacteroides infection observed. Major lesions caused by Bacteroides described elsewhere, but not observed within the Stanford University Hospitals, included endocarditis,[34] appendicitis,[13b] chronic ulcerative colitis [36] and possibly those of Reiter's disease.[6a]

A considerable number of Bacteroides infections have undoubtedly been overlooked in this hospital. Bacteremias and septicemias in particular have probably been missed. Whereas common technics are of some value,[37] the effective isolation of Bacteroides from the blood stream requires special anaerobic methods.[6] Even highly specialized anaerobic technics of blood culture may not suffice for the recognition of mild, atypical bacteremias, which are commoner than was previously supposed.[2] Considerable diagnostic aid by a serum flocculation method purportedly specific for Bacteroides funduliformis antibodies has been reported.[38] An alcoholic extract of the organism is the antigen employed.

Metastatic, suppurative local lesions may occur during generalized sepsis,[8b] as the result of infected emboli arising in a suppurative form of thrombophlebitis. Mild, evanescent bacteremias, often not recognized, have been stated to result in commonly observed small, isolated abscesses.[2] The original foci of Bacteroides bacteremias are supposedly in areas where Bacteroides maintain a saprophytic existence within the natural cavities of the body.[39] However, evidence suggesting exogenous infection by means of contaminated water has been presented.[6b] Transmission of the organism from patient to patient has been indicated [40]: In a group of soldiers, deep gunshot wounds became infected by Bacteroides in a hospital. It has been stated that secondary infection is commonly caused by Bacteroides,[26b] particularly in neoplastic disease.[17] This study tended to support the validity of these claims.

The formation of gas by Bacteroides in culture has been demonstrated.[41] One instance of gas formation in vitro was observed in this series (by the organism isolated in case 14). Cunningham [42] noted the

36. Dack.[8] Dack, G. M.; Dragstedt, L. R., and Heinz, T. E.: Bacterium Necrophorum in Chronic Ulcerative Colitis, J. A. M. A. **106**:7 (Jan. 4) 1936.

37. Pham.[6b] Waring, J. J.; Ryan, J. G.; Thompson, R., and Herrell, W. E.: Bacteroides Septicemia: Report of Case with Recovery, Laryngoscope **53**:717, 1943.

38. Lemierre.[2] Laporte, A., and Brocard, H.: La réaction de floculation du sérum en présence d'un extrait alcoolique microbien dans les infections à Bacillus funduliformis, Compt. rend. Soc. de biol. **131**:4, 1939.

39. Smith and Ropes.[6a] Lemierre.[8b]

40. Bogdan, A.: Eine bisher unbekannte Infektionshkrankheit bei Verwundeten, Med. Klin. **12**:383, 1916.

41. Chandler and Breaks.[18] Harris and Brown.[27]

42. Cunningham, J. S.: Human Infection with Actinomyces Necrophorus: Bacteriologic and Pathologic Report of Two Cases Terminating Fatally, Arch. Path. **9**:843 (April) 1930.

presence of gas, both clinically and roentgenologically, in a case of retropharyngeal abscess due to Bacteroides which terminated fatally. The presence of gas in the tissues of the arm was noted by Smith and Ropes [6a] during the course of a fatal sepsis. Clinically, typical gas gangrene with roentgen evidence of gas in the tissues was observed in case 22 of the present series. This evidence indicates that Bacteroides infection must be considered in the differential diagnosis of gas gangrene.

Available data indicate that Bacteroides is resistant to penicillin and streptomycin, and evidence in this study suggests that the clinical response to the administration of these antibiotic drugs may be poor. Consideration must be given to the possibility of superimposed or concomitant infection by penicillin-resistant Bacteroides or other organisms complicating the treatment of disease presumably caused by penicillin-sensitive bacteria.[43]

SUMMARY

1. Bacteroides was recovered in 47 cases. A considerable variation in the severity of disease caused by this organism was demonstrated.

2. The most common sources were localized superficial lesions and the female genital tract. Bacteroides was also isolated in cases of bacteremia, meningitis, empyema, lung abscess, bronchiectasis, infection of the urinary tract, chronic otitis media, maxillary sinusitis, osteomyelitis, cervical sinuses, abdominal abscesses and thyroiditis.

3. Bacteroides was frequently isolated in pure culture, but the concurrent recovery of anaerobic streptococci was of significant frequency.

4. Bacteroides has gas-forming tendencies and may produce lesions which simulate those of gas gangrene.

5. There is clinical and laboratory evidence that a considerable degree of resistance to penicillin and streptomycin may be an important characteristic of Bacteroides.

43. Weinstein, L.: The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin, Am. J. M. Sc. **214**:56, 1947. Appelbaum, E., and Leff, W. A.: Occurrence of Superinfections During Antibiotic Therapy, J. A. M. A. **138**:119 (Sept. 11) 1948.

MYOCARDIAL INFARCTION

Observations on One Hundred Patients Who Survived up to Six Years

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IN 1947, Mintz and Katz [1] published observations on a large series of patients with recent myocardial infarction and pointed out features of importance in establishing the immediate prognosis. Recently, we [2] analyzed the factors involved in determining the long term prognosis. During the latter study, a follow-up survey was made on 100 patients who had survived acute myocardial infarction from one to six years. The present report correlates the degree of electrocardiographic restitution following acute infarction with the clinical state of the patient.

The necessary data were obtained for 100 patients of the 507 whose cases had previously been reported.[2] Of these, 84 were interviewed and examined at the hospital; for the remaining 16, follow-up information and electrocardiograms were obtained from the records of their private physicians. In every instance, a new electrocardiogram was taken and interpreted by us.

Almost all the patients interviewed were maintained on a regimen of combinations of barbiturates, papaverine and/or glyceryl trinitrate. One patient in the fourth decade who was addicted to the use of morphine had been treated for the habit before infarction. Most of the patients had returned to their former jobs and were working about the same number of hours as before infarction. In most instances, the younger patients were able to resume a fuller share of activity after recovery than the

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1. Mintz, S. S., and Katz, L. N.: Recent Myocardial Infarction: An Analysis of Five Hundred and Seventy-Two Cases, Arch. Int. Med. **80**:205 (Aug.) 1947.

2. Katz, L. N.; Mills, G. Y., and Cisneros, F.: Observations on the Survival of Patients After Recent Myocardial Infarction, to be published.

older ones. This was also observed by Cooksey,[3] Master and Dack [4] and others.[5]

TYPES OF ELECTROCARDIOGRAPHIC RESTITUTION

Patients were classified according to the degree of recovery shown in follow-up electrocardiograms. Three classifications were used:

1. *Little Electrocardiographic Restitution* (figure, *A*).—The electrocardiograms for this group showed changes similar to those observed at the time of infarction, with characteristic coronary contours of the S-T segment of the T wave and of the QRS complex. The coronary patterns were obvious and could readily be classified into one of the types previously recognized by one of us (L. N. K.).[6]

2. *Partial Electrocardiographic Restitution* (figure, *B*).—The electrocardiograms for this group showed the QRS complex, and sometimes the T wave, characteristic of the coronary patterns, but without the deviations in the S-T segment. Thus, there had been some return toward normal.

3. *Complete Electrocardiographic Restitution* (figure, *C*).—The electrocardiograms for this group were similar to the control records, were within normal limits or, if abnormal, showed no stigma of coronary insufficiency.

The groups with little and partial restitution were those to which we gave the electrocardiographic designation of chronic coronary insufficiency.

RELATIONSHIP OF ELECTROCARDIOGRAPHIC RESTITUTION TO CLINICAL FINDINGS

1. *Little Electrocardiographic Restitution.*—Seventy-seven of the 100 patients (59 males and 18 females) had little electrocardiographic restitution. Twenty-four of these had no evidence of angina, hypertension or heart failure. In the follow-up, hypertension occurring alone was the most frequent finding (16 cases); with angina pectoris, it accounted for the most frequent combination (15 cases). Angina pectoris alone accounted for 11 cases. Heart failure was observed alone in 1 case, and in various combinations in the remaining 10. None of the patients had heart failure as an isolated disorder on admission to the hospital, but in the 3 instances in which it was present at that time it was associated with angina or hypertension. Twelve patients had heart failure at follow-up, and for 11 of these the electrocardiograms showed little restitution.

2. *Partial Electrocardiographic Restitution.*—Fourteen patients (9 males and 5 females) had partial electrocardiographic restitution at follow-up. Four of these

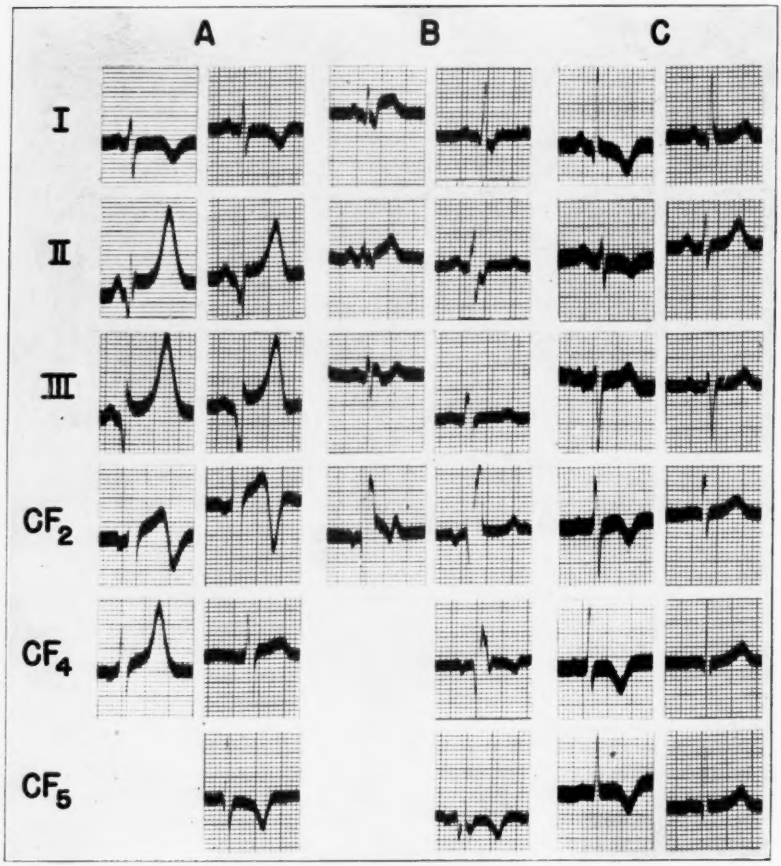
3. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Especial Reference to Prognosis, J. A. M. A. **104**:2063 (June 8) 1935.

4. Master, A. M., and Dack, S.: Rehabilitation Following Acute Coronary Artery Occlusion, J. A. M. A. **115**:828 (Sept. 7) 1940.

5. (*a*) King, H. C.: Prognosis in Coronary Heart Disease and After Coronary Occlusion, Ohio State M. J. **33**:524, 1937. (*b*) Master, A. M.; Jaffe, H. L., and Dack, S.: The Treatment and Immediate Prognosis of Coronary Artery Thrombosis, Am. Heart J. **12**:549, 1936. (*c*) Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis—an Analysis of Two Hundred and Eighty-Seven Cases, ibid. **5**:705, 1930.

6. Katz, L. N.: Electrocardiography Including an Atlas of Electrocardiograms, ed. 2, Philadelphia, Lea & Febiger, 1946.

showed no evidence of hypertension, angina or heart faliure. Angina pectoris and hypertension appeared alone in 3 cases each, and in combination in 3 cases. One patient suffered from angina and heart failure. None of the patients in this group had heart failure at the time of admission.



A, electrocardiogram of a white man of 33. The first record was taken on June 2, 1941, ten days after the clinical episode. The follow-up record was taken on March 13, 1947. There is little restitution. *B*, a white man of 60. The first record was taken on March 7, 1940, one day after the clinical episode. The follow-up record was taken on March 5, 1947. There is partial restitution. Evidence of the healed infarct is shown by the deep Q wave in CF_2 and CF_4. *C*, a white woman of 68. The first record was taken on October 8, 1943, two weeks after the clinical episode. The follow-up record was taken on March 13, 1947. There is complete restitution.

3. *Complete Electrocardiographic Restitution.*—Only 9 of the 100 patients examined had complete electrocardiographic restitution. Eight were males. Four of these had no hypertension, angina or heart failure, and 4 had clinical hypertension only. The remaining patient had angina pectoris. None of this group had heart failure on admission.

Because the number of patients with partial and complete restitution was small it would not be warranted to draw a statistical correlation. However, in the two groups together there were 23 patients, and of these 8, or 35 per cent, had no hypertension, angina or heart failure at follow-up. This figure is comparable to that for the group with little restitution, in which 24 of 77 patients (31 per cent) had no sequelae. Our breakdown indicates that hypertension and angina pectoris are

Distribution of the 100 Patients at the Time of Follow-Up

	No Angina, Hypertension or Failure	Angina Alone	Hypertension Alone	Failure Alone	Angina, Hypertension and Failure	Angina and Hypertension	Hypertension and Failure	Angina and Failure	Totals
Little electrocardiographic restitution									
Males	19	9	14	0	2	10	2	3	59
Females	5	2	2	1	1	5	2	0	18
Totals	24 (31.2%)	11 (14.3%)	16 (20.8%)	1 (1.3%)	3 (3.9%)	15 (19.4%)	4 (5.2%)	3 (3.9%)	77 .....
Partial electrocardiographic restitution									
Males	4	2	0	0	0	2	0	1	9
Females	0	1	3	0	0	1	0	0	5
Totals	4 (28.7%)	3 (21.4%)	3 (21.4%)	0	0	3 (21.4%)	0	1 (7.1%)	14 .....
Complete electrocardiographic restitution									
Males	4	1	3	0	0	0	0	0	8
Females	0	0	1	0	0	0	0	0	1
Totals	4 (44.4%)	1 (11.1%)	4 (44.4%)	0	0	0	0	0	9 .....
Totals	32	15	23	1	3	18	4	4	100

most frequently noted clinically in the follow-up examination of the patient with myocardial infarction.

There was little difference in the rate of occurrence of angina among patients with little, partial or complete restitution. In general, the distribution of angina and hypertension, alone or in combinaiton, was about the same in the three groups classified according to degree of electrocardiographic restitution. Heart failure, alone or in combination with angina and/or hypertension, was limited almost entirely (in 11 of 12 cases) to the group with little restitution.

HYPERTENSION

Forty-eight patients had hypertension alone or in combination with heart failure and/or angina; of these, 15 were females and 33 males (a somewhat higher ratio of females to males than in the total group

studied). In the cases of those patients whose blood pressure levels previous to infarction were known, the trend was toward a higher blood pressure level at the time of the follow-up. Master and his associates [7] reported a return of hypertension in two thirds of their cases. Chambers [8] pointed out that 58 per cent of his patients regained the hypertension by the end of the second year and that in those cases in which the blood pressure had not returned to hypertensive levels by the end of the first year there was a greater variety of complaints. In our experience, all the patients who had hypertension at follow-up one year or more after infarction had a history of hypertension before infarction, and of these 18 had coexisting angina pectoris.

Of the patients in the 23 cases of uncomplicated hypertension, 12 had the pattern of an infarct of the posterior wall; 8, that of an infarct of the anterior wall; 1, that of an infarct of the lateral wall, and 2 that of an atypical infarct. Sixteen of these patients had no defect of impulse initiation or conduction and no low voltage in the follow-up electrocardiogram. There were 4 instances of conduction disturbances; all were in cases of intraventricular block. Disturbances of impulse initiation were seen in 3 cases in which the patients had ventricular premature systoles, and in a fourth in which the patient had nodal premature systoles together with intraventricular block.

ANGINA PECTORIS

Fifteen patients, 12 of whom were males, had only angina pectoris at follow-up. Angina occurred alone with almost the same frequency in patients who had anterior wall infarct patterns or posterior wall infarct patterns, viz., in 4 of the former and 5 of the latter. Angina occurred in 3 cases in which patients showed lateral wall infarct patterns and in 3 cases in which the pattern was atypical. Of these 15 patients who had angina without hypertension or heart failure, 11 showed little electrocardiographic restitution, 3 partial restitution and 1 complete restitution. Therefore, there is no actual relationship between the various types of electrocardiographic restitution and the clinical syndrome of angina pectoris: It appears in patients with complete restitution as well as in those with partial or little restitution.

Considering all 39 cases of anginal syndrome in the groups with little and partial restitution (which included 91 cases), an interesting fact appeared. These groups were those in which the electrocardiographic diagnosis was chronic coronary insufficiency. Thus, more than

7. Master, A. M.; Jaffe, H. L.; Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During and After Coronary Occlusion, Am. Heart J. **26**:92, 1943.

8. Chambers, W. N.: Blood Pressure Studies in One Hundred Cases of Coronary Occlusion with Myocardial Infarction, Am. J. M. Sc. **213**:1, 1947.

1 in 3 of our patients with the electrocardiographic pattern of chronic coronary insufficiency had a clinical syndrome of angina.

There were 11 patients in this group who had no disturbance of impulse origin or conduction. Three patients had intraventricular block, associated in 1 case with auricular premature systoles and in 1 with ventricular premature systoles. One patient had auricular premature systoles alone. Low voltage was observed once.

HEART FAILURE

Heart failure alone was observed only once at follow-up, but it was present 11 times in association with hypertension, angina or both. It occurred with almost the same frequency in association with angina pectoris as with hypertension. The 1 occurrence of isolated heart failure was in a female patient. Although the presence of heart failure is a grave sign, the degree of failure present was minimal except in 1 instance. This patient, who had moderately severe failure, was not receiving digitalis; the blood pressure was 300 systolic and 110 diastolic, and the electrocardiogram was grossly abnormal. Except in 1 instance, all the patients with heart failure showed little electrocardiographic restitution. The 1 patient had angina, associated with heart failure and with partial electrocardiographic restitution.

It should be pointed out that digitalization is indicated when the patient has had an infarct and survives, and when heart failure develops for reasons other than that of a new infarct. Even when heart failure is due to a new infarct adequate digitalization is not contraindicated and is without hazard when properly employed.

Heart failure was observed in the cases of 5 patients with previous posterior wall infarct patterns, in those of 2 patients with anterior wall infarct patterns, in those of 2 patients with lateral wall infarct patterns and in those of 3 patients with atypical patterns. The electrocardiogram of 1 patient, who was in congestive heart failure without angina or hypertension, showed low voltage. This was the only defect in impulse initiation or conduction noted in cases in which patients had heart failure. Such abnormalities of impulse initiation as ventricular, nodal and auricular premature systoles represent a potential hazard since more serious ectopic rhythms, such as auricular fibrillation, ventricular tachycardia or ventricular fibrillation, may develop later, with the hazard in the case of the latter two of unexpected death. Patients with the latter conditions should receive quinidine.

COMBINATION OF HYPERTENSION, ANGINA PECTORIS AND HEART FAILURE

In our series, 20 males and 9 females had some combination of angina, failure and/or hypertension. Angina and hypertension was the most frequent combination; it occurred in 18 cases, in 15 of which

patients had little electrocardiographic restitution. None of the patients with complete electrocardiographic restitution had combinations of these conditions; however, it must be remembered that there were only 9 patients in that group.

Of the 29 patients with more than one clinical condition at follow-up, at the time of infarction 8 had anterior wall infarct patterns, 11 posterior wall infarct patterns, 7 lateral wall infarct patterns and 3 atypical infarct patterns. Two of the patients had intraventricular block, which in 1 instance occurred with auriculoventricular block. One patient who had ventricular premature systoles also had auricular fibrillation. The fibrillation and an atypical infarct pattern were present at the time of hospitalization, and at follow-up there was little electrocardiographic restitution. One other instance of auricular fibrillation was noted; this, too, was in a case with little restitution. Low voltage was observed in 2 instances. Twenty-one patients had no defects of impulse initiation or conduction. Their tracings were all consistent with the electrocardiographic diagnosis of chronic coronary insufficiency.

ABSENCE OF HYPERTENSION, ANGINA PECTORIS AND HEART FAILURE

Thirty-two patients (27 males and 5 females) were found to have no angina, heart failure or hypertension at follow-up. Most of these patients had either anterior wall infarct patterns (18 patients) or posterior wall infarct patterns (12 patients). Disturbances of impulse initiation and conduction occurred with almost the same frequency in this group as in the group with hypertension alone. There were 3 instances of intraventricular block, 1 associated with auriculoventricular block and 1 with ventricular premature systoles. In 2 instances, the electrocardiogram showed little restitution; 1 patient had intraventricular block alone, and 1 had both intraventricular and auriculoventricular block. Conduction disturbances, all ventricular premature systoles, occurred in 3 cases. Low voltage was observed 4 times as an isolated disturbance. Twenty-two patients had defects of impulse initiation or conduction.

COMMENT

It is of considerable interest and importance that of 100 patients examined one to six years after infarction, 77 had little electrocardiographic restitution and only 9 had complete restitution. It is evident that the electrocardiographic pattern can prognosticate neither survival nor rehabilitation, for the greastest percentage of surviving patients had the most abnormal records and all the patients had resumed their previous occupations. Physicians must be cognizant of the large number of patients whose electrocardiograms made after infarction will show little change in contour from the pattern of recent infarction over a period of years. The cause of episodes of precordial pain in these

patients may be misdiagnosed as recent infarction on the basis of the electrocardiogram unless serial records are made. Comparison of the frequency of clinical angina pectoris with the large number of tracings which indicate the electrocardiographic diagnosis of chronic coronary insufficiency demonstrates the correlation between these two distinct entities in patients surviving infarction.

The clinical state of the patient can be anticipated in some respects with the aid of the electrocardiogram. Among our 100 patients, the number without hypertension, angina pectoris or heart failure was about equal in the two groups of those with little electrocardiographic restitution and those with partial and complete restitution. Angina pectoris and hypertension, singly or in combination, occurred without statistical differences in the three groups classified according to electrocardiographic restitution. Heart failure was the only entity which was heavily concentrated in one group. Alone, or in combination with angina pectoris and hypertension, it was present in 11 patients with little restitution and only once in the group showing partial restitution. Heart failure associated with acute myocardial infarction enhances the gravity of the prognosis.[2] Only 3 of our 100 patients exhibited heart failure on admission. The fact that 11 patients with heart failure on follow-up were in the group with little restitution would indicate that in this one respect the electrocardiogram which changes little after acute infarction carries with it special importance. For this reason it is justifiable to be more optimistic when there is complete electrocardiographic restitution after infarction. The occurrence of clinical angina in 39 patients of 91 whose condition was electrocardiographically diagnosed as chronic coronary insufficiency (little or partial restitution) indicates the frequency of the association of clinical angina with the electrocardiographic pattern of chronic coronary insufficiency in patients surviving myocardial infarction.

SUMMARY AND CONCLUSIONS

One hundred patients were examined who had survived one to six years after acute myocardial infarction.

The electrocardiograms of 77 of these 100 patients showed little restitution, those of 14 showed partial restitution and those of 9 showed complete restitution.

The electrocardiographic pattern after infarction did not prognosticate survival of the patient.

Heart failure appeared almost entirely in the group of patients with little electrocardiographic restitution.

The electrocardiographic diagnosis of chronic coronary insufficiency is distinct from the clinical syndrome of angina; yet, clinical angina occurred in 43 per cent of patients surviving infarction whose electrocardiographic pattern was that of chronic coronary insufficiency.

INTRAVENOUS CATHETERIZATION OF THE HEART IN SUSPECTED CONGENITAL HEART DISEASE

Report of Seventy-Two Cases *

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RECENT advances in the surgical alteration [1] and correction of certain congenital defects of the heart and the great vessels make it imperative that more exact diagnoses of such lesions be made. Intravenous catheterization ot the heart has been found to be a most useful aid in ascertaining the condition when such congenital abnormalities are suspected. Forssmann,[2] in 1929, first introduced the method by catheterizing his own heart. In 1941, Cournand and Ranges [3] emphasized its applicability to the study of certain physiologic changes that occur in various types of heart disease. Blood samples may be obtained from various parts of the venous system, from the right side of the heart and from the pulmonary artery and its branches for estima-

* Reports of 23 of the cases were used in a preliminary report.

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From the Departments of Internal Medicine, Pharmacology and Roentgenology, Baylor University College of Medicine.

1. (*a*) Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus: Report of First Successful Case, J. A. M. A. **112**:729 (Feb. 25) 1939. (*b*) Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, ibid. **128**:189 (May 19) 1945. (*c*) Crafoord, C., and Nylin, S.: Congenital Coarctation of the Aorta and Its Surgical Treatment, J. Thoracic Surg. **14**:347, 1945. (*d*) Gross, R. E., and Hufnagel, C. A.: Coarctation of the Aorta: Experimental Studies Regarding Its Surgical Correction, New England J. Med. **233**:287, 1945.

2. Forssmann, W.: Die Sondierung des rechten Herzens, Klin. Wchnschr. **8**:2085, 1929.

3. Cournand, A., and Ranges, H. A.: Catheterization of Right Auricle, Proc. Soc. Exper. Biol. & Med. **46**:462, 1941.

tion of the oxygen content. At the same sites, the blood pressure may be determined with a Hamilton manometer [4] or similar apparatus. Other investigators [5] have used this method to study the hemodynamics in various derangements of the cardiorespiratory system. The purpose of the present paper is to present the results of intravenous catheterization of the heart in 72 cases of suspected congenital heart disease.

The normal variation of the oxygen content in the various chambers of the heart has been established by Dexter and others.[6] The normal variation between the superior vena cava and the right atrium auricle is 1.9 volumes per cent; between the right atrium and the right ventricle, 0.9 volumes per cent; between the right ventricle and the pulmonary artery, 0.5 volumes per cent, and within the pulmonary branches themselves, 0.4 volumes per cent.

The technic as described by Cournand [7] and his group of workers has been used by us with certain modifications to meet specific problems. We administer penicillin prophylactically for twelve hours before the procedure, and a sufficient dose of barbiturates for adequate sedation of the patient is given one to two hours before the examination. An antecubital vein is exposed with aseptic technic, and a small incision is made in its wall. A special radiopaque ureteral catheter (no. 6 F. or 9 F.) with a curved tip and with a hole in its end is introduced into the vein and passed through the subclavian vein, the superior vena cava, the right atrium and the right ventricle and into the pulmonary artery and its branches whenever possible (fig. 1). In some instances, the catheter may pass into an anomalous pulmonary vein emptying into

4. Hamilton, W. F.; Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal: I. Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**:427, 1934.

5. Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: The Effect of Venesection and the Pooling of Blood in Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observation in Acute Circulatory Collapse in Three Instances, J. Clin. Investigation **24**:337, 1945. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technique of Right Atrial Catheterization, ibid. **24**:332, 1945. Brannon, E. S.; Stead, E. A., Jr.; Warren, J. V., and Merrill, A. J.: Hemodynamics of Acute Hemorrhage in Man, Am. Heart J. **31**:407, 1946.

6. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Sagerson, R. P., and Evans, J. M.: Studies of Congenital Heart Disease: II. The Pressure and Oxygen Content of Blood in the Right Auricle, Right Ventricle, and Pulmonary Artery in Control Patients, with Observations on the Oxygen Saturation and Source of Pulmonary "Capillary" Blood, J. Clin. Investigation **36**:554, 1947.

7. Cournand, A.; Riley, R. L.; Breed, E. S.; Baldwin, E. deF., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24**:106, 1945.

the right atrium through a septal defect, into the left side of the heart and, possibly, into the pulmonary veins or into the aorta. The catheter is under fluoroscopic guidance at all times.

Throughout the procedure, an extremely slow drip of isotonic sodium chloride solution containing heparin sodium is maintained through the catheter to prevent clotting of the blood in the lumen. After the tip

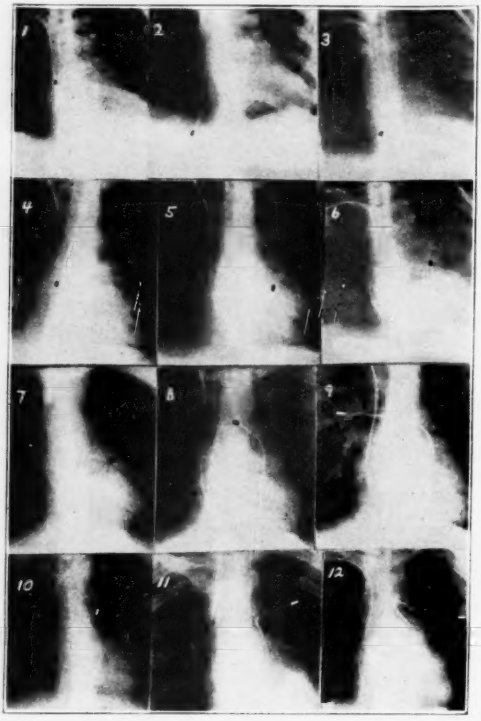

Fig. 1.—Positions of tip of catheter: *1*, superior vena cava; *2*, inferior vena cava; *3*, right atrium; *4*, right atrium; *5*, right ventricle; *6*, right ventricle; *7*, right ventricle near pulmonary conus; *8*, proximal portion of right pulmonary artery; *9*, right pulmonary artery; *10*, left pulmonary artery; *11*, left pulmonary artery, and *12*, distal portion of left pulmonary artery.

of the catheter has reached the desired spot, several cubic centimeters of blood is withdrawn through the catheter and discarded to avoid any dilution with the sodium chloride solution. Samples of blood are then withdrawn into oiled syringes and stored under oil in iced containers. They are analyzed for oxygen and carbon dioxide content by

the manometric method of Van Slyke and Cullen.[8] Samples are drawn from all the aforementioned areas whenever possible. Roentgenograms are obtained to establish each position of the catheter. Pressures are recorded by connecting the catheter to a Hamilton optic manometer. The patients are given penicillin for forty-eight hours after the procedure.

REPORT OF CASES

To date, 72 cases have been studied by this procedure. The following is a summary of the resulting diagnoses.

- Acyanotic conditions
  - Coarctation of the aorta, 3 cases (1 complicated with a patent ductus arteriosus)
  - Essential (idiopathic) pulmonary hypertension, 2 cases
- Potentially cyanotic conditions
  - Interatrial septal defect, 8 cases
  - Interventricular septal defect, 15 cases
    - Uncomplicated, 13 cases
    - Interventricular septal defect, common truncus arteriosus and pulmonary arteriovenous aneurysm, 1 case
    - Interventricular septal defect and an associated patent ductus arteriosus, 1 case; operation performed
    - Interventricular septal defect with right arched aorta, 1 case
  - Patent ductus arteriosus, 22 cases; diagnosis confirmed in the 18 cases in which operation has been performed to date
- Cyanotic conditions
  - Tetralogy of Fallot, 5 cases; diagnosis confirmed at operation
  - Tetralogy of Fallot with patent ductus arteriosus, 1 case; operation not performed
  - Common atrium with possible tricuspid atresia, 1 case
- Special conditions
  - Dilated pulmonary artery with hypoplastic aorta, 1 case
  - Pulmonary arteriovenous aneurysm, 1 case; findings at catheterization normal
- Normal heart, 9 cases; congenital heart disease suspected; normal pressures and gas values observed on catheterization
- Diagnosis impossible because of insufficient data, 3 cases

A few of our cases are presented in more detail with comments to illustrate some of the special features one may encounter:

Acyanotic Conditions.—Coarctation of the Aorta: Two patients with uncomplicated coarctation of the aorta, the diagnosis in both cases having been proved at operation, were catheterized. In neither case was there significant alteration of

8. Peters, J. P., and Van Slyke, D. D.: Methods, in Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 2.

the oxygen content or of pressures. The coarcted site, in cases of this type, may be studied roentgenographically by the injection of a 70 per cent solution of iodopyracet injection (diodrast®) through a catheter introduced into the proximal portion of the aorta via the carotid or brachial arteries.

Catheterization in a third case, in which a combination of patent ductus arteriosus and coarctation of the aorta existed, yielded the following data:

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	12.5	.....
Right atrium	12.74	0/—3
Right ventricle	12.25	90/2
Right pulmonary artery	18.30	88/70

Idiopathic Pulmonary Hypertension: S. D., a girl of 4, was admitted to the hospital for evaluation of a heart murmur which had been known to be present since she was 7 months old. She had not been born a blue baby and had had no episodes of cyanosis. She had shown no limitation of her physical or mental development and was able to keep up with her own age group in participation in games.

Physical examination showed a slender, well developed, acyanotic girl with ptosis of the left eyelid. There was no clubbing. The blood pressure was 125 systolic and 75 diastolic. Examination of the heart revealed a somewhat overaccessible right ventricle and some enlargement of the left side of the chest anteriorly. The left border of the heart was at the anterior axillary line. There was a sinus rhythm, the rate being 96 beats per minute. A harsh, grade 5 systolic murmur was heard over the entire precordium, the maximum intensity being in the second left interspace. No diastolic murmur was heard. Electrocardiograms revealed right axis deviation. Roentgenograms showed evidence of enlargement of the right atrium and the inflow tract of the right ventricle.

Venous catheterization studies revealed essentially the same oxygen content (13.3 volumes per cent) in the superior vena cava, the right atrium, the right ventricle and the main and right pulmonary arteries. The blood pressure in the right atrium was normal, but in the right ventricle readings of 86 systolic and 40 diastolic and 86 systolic and 60 diastolic were made, and in the pulmonary artery 112 systolic and 60 diastolic and 98 systolic and 62 diastolic.

A diagnosis of idiopathic pulmonary hypertension was made. No evidence of a left to right shunt was noted. No operation was performed.

A similar case of pronounced increase in pressure in the right ventricle and the pulmonary artery pressure was in an acyanotic child with a systolic murmur. This patient, likewise, showed no evidence of left to right shunt. The cause of the increased pulmonary hypertension was not obvious on either physical or roentgen examination.

Potentially Cyanotic Conditions.—Interatrial Septal Defect: S. A. was a white woman of 24 who had been told early in life that she had a heart murmur. For the past year she had been experiencing increasing tiredness, and for the past six months exertional dyspnea had developed, but on no occasion had she noted cyanosis. There had been no swelling of the ankles or nocturnal dyspnea. There was a loud, harsh systolic murmur, heard over the entire precordium but with its loudest intensity in the second left interspace at the parasternal line. It was accompanied with a palpable thrill. The systolic arterial pressure was 120 and the diastolic pressure was 75. There was no stunting of growth, no cyanosis or clubbing and no evidence of decompensation. Roentgenograms revealed a sug-

gestion of anterior bulging of the heart in the left anterior oblique position and some enlargement of the right heart in posterior-anterior films. The pulmonary artery appeared somewhat dilated, and there was a suggestion of a "hilar dance" on fluoroscopic examination. Right axis deviation was noted on the electrocardiographic tracing.

Catheterization studies of the heart in this case yielded the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %
Superior vena cava	10.9	34.5
Inferior vena cava	10.4	34.2
Right atrium	13.7	26.0
Right ventricle	13.8	26.6
Right pulmonary artery	13.6	26.4

D. L., a schoolboy of 7, was referred for study after the detection of a heart murmur by the school physician. The patient had always been under average size, but alert and active. The mother denied that the child was ever cyanotic or dyspneic; he ran as long and as fast as his friends.

Physical examination showed an undernourished, undersized, active boy. The blood pressure in both arms was 100 systolic and 65 diastolic; after exercise it was 100 systolic and 30 diastolic. A slight prominence of the left side of the thorax was noted. The left border of cardiac dulness was within normal limits. A blowing systolic murmur was heard loudest in the first and second interspaces between the sternum and the midclavicular line and was well transmitted over the entire precordium to the axillas and over the shoulder strap areas to the intrascapular area. The second pulmonic sound was slightly accentuated. There was no cyanosis or clubbing. A fluoroscopic examination showed moderate prominence of the pulmonary artery and a suggestion of a "hilar dance." The electrocardiogram revealed right axis deviation.

Heart catheterization studies in this case revealed an increase of oxygen of 4.9 volumes per cent from the superior vena cava to the right atrium. The blood pressures were recorded as 5 systolic and 2 diastolic in the right atrium, 34 systolic and 5 diastolic in the right ventricle and 34 systolic and 5 diastolic in the right pulmonary artery.

Atrial septal defects can usually be diagnosed by noting the signicant increase in the oxygen content of the blood from the right atrium as compared with that of the blood from the venae cavae. This results from the shunting of blood from the left atrium to the right atrium. Unusual defects, such as the draining of the pulmonary vein into the right atrium, may occasionally be encountered. An increase in the oxygen content from the atrium to the pulmonary vein as well as roentgenographic evidence of the position of the catheter (fig. 2) will establish the diagnosis. In this instance, the oxygen content of the right atrium was 13.3 volumes per cent, and that of the pulmonary vein, 21.6 volumes per cent. Brannon, Weens, and Warren[9] found that a diagnosis of

9. Brannon, E. S.; Weens, H. S., and Warren, J. R.: Atrial Septal Defect: Study of Hemodynamics by the Technique of Right Heart Catheterization, Am. J. M. Sc. **210**:480, 1945.

interatrial septal defect could be made by introducing the catheter through the septal defect or by observing a significant increase in the oxygen content of the blood in the right atrium as compared with that obtained from the superior vena cava. The former method, however, has been unsuccessful in the majority of cases. Baldwin, Moore and

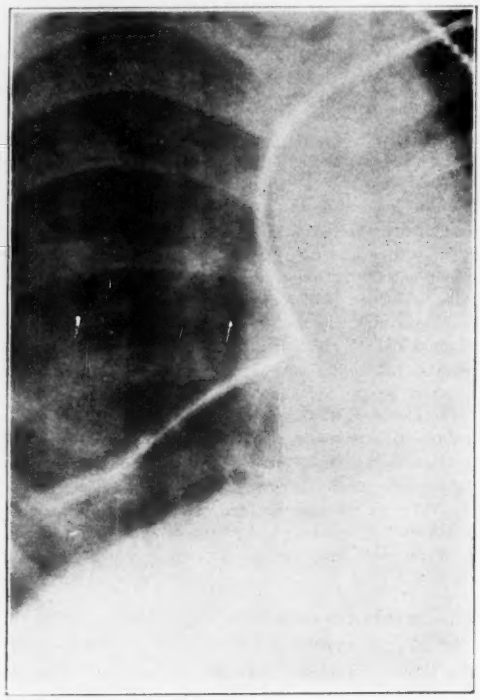

Fig. 2.—Tip of catheter in a pulmonary vein communicating with the right atrium.

Noble [10] observed an instance in which tricuspid insufficiency associated with an interventricular septal defect gave a significant rise in the oxygen content of the right atrium. The authors recognized the disorder by an analysis of the atrial and ventricular pressure tracings.

10. Baldwin, E. deF.; Moore, L. V., and Noble, R. P.: The Demonstration of Ventricular Septal Defect by Means of Right Heart Catheterization, Am. Heart J. **32**:152, 1946.

as described by Cournand.[11] Considerable variation in the pressure in the right ventricle has been noted, a low pressure of 23 systolic and 3 diastolic and a high pressure of 87 systolic and 8 diastolic having been recorded in the pulmonary arteries; a low pressure of 20 systolic and 8 diastolic and a high pressure of 87 systolic and 6 diastolic were noted on one occasion.

Interventricular Septal Defect.—Uncomplicated: R. B. was a boy of 4 whose parents had been told that he had congenital heart disease at the age of 2 months. However, the child had continued to develop normally both physically and mentally, and there had been no retardation of his activities. He had experienced no dyspnea, cyanosis or periods of syncope.

Physical examination showed a slender, alert white boy of 4. There was no evidence of clubbing of the finger nails or cyanosis. A systolic thrill was felt in the third left interspace, and a harsh systolic murmur, heard all over the precordium, reached its maximum in the second left interspace. There was no cardiac enlargement. Roentgenograms revealed no definite cardiac enlargement, and no "hilar dance" was noted on fluoroscopic examination. An electrocardiographic tracing was well within normal limits.

Catheterization studies revealed the following data:

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	12.13	.....
Right atrium	12.60	2/0
Right ventricle	16.44	77/16
Right pulmonary artery	16.40	.....
Aorta	18.88	80/52

The catheter was passed through the ventricular septal defect, out through the aorta and into the left subclavian artery (fig. 3).

The recognition of an interventricular septal defect by venous catheterization can be made on the observation of a significant increase in the amount of oxygen in the right ventricle as compared with that in the right atrium or on passing the catheter through a septal defect into the left ventricle and out through the aorta. Immediately as the catheter enters the systemic side an increase in systolic and diastolic pressure is noted.

Associated with Other Defects: A significantly elevated oxygen content of the blood in the right ventricle may reflect the presence of an interventricular septal defect or, theoretically, a patent ductus with associated incompetency of the pulmonic valve. Three instances of the latter phenomenon were suspected by Dexter and his associates.[12] In 1 of their cases, after surgical intervention which eradicated all

11. Cournand, A.; Lauson, H. D.; Bloomfield, R. A.; Breed, E. S., and Baldwin, E. deF.: Recording of Right Heart Pressures in Man, Proc. Soc. Exper. Biol. & Med. **55**:34, 1944.

12. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Sosman, M. C., and Evans, J. M.: Studies of Congenital Heart Disease: III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy, Ventricular Septal Defect, and Auricular Septal Defect, J. Clin. Investigation **26**:561, 1947.

murmurs, venous catheterization failed to reveal any significant variation of oxygen content in the right atrium, the right ventricle or the pulmonary artery. They stated the belief that a diagnosis of interventricular septal defect in the presence of a patient ductus should be made with caution.

Associated with Common Truncus Arteriosus and Pulmonary Arteriovenous Aneurysm: C. A. D.'s parents had been told that the child had a heart murmur

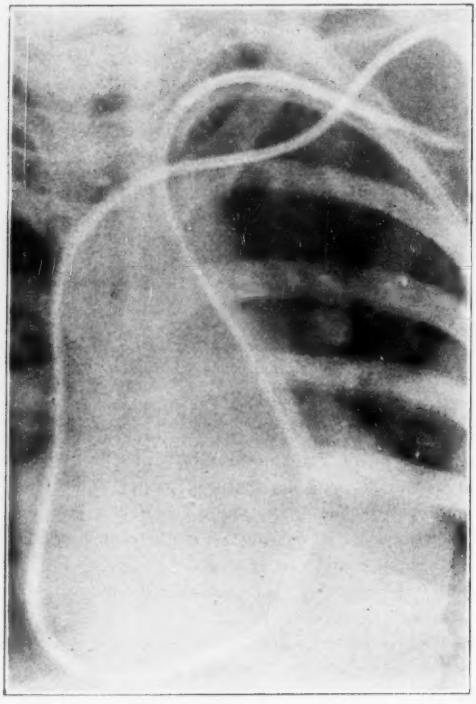

Fig. 3.—Tip of catheter in the left subclavian artery, having passed through a ventricular septal defect.

at 5 months. The mother had had German measles when she was six weeks pregnant. The child had been slow to develop both physically and mentally and recently had been found to have bilateral eighth nerve deafness. There had been no definite episodes of cyanosis. Physical examination showed a small, undernourished child. The left border of the heart was at the anterior axillary line. A harsh, systolic murmur with its maximum intensity in the first and second left interspaces was heard over the entire precordium; it was transmitted to the left side and to the back. There was a late systolic accentuation with a

short diastolic component. Fluoroscopic examination showed a questionable enlargement of the left ventricle and the right atrium. The pulmonary conus was prominent.

Catheterization studies of the heart revealed the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %
Superior vena cava	12.07	34.5
Right atrium	11.84	35.9
Right ventricle	17.03	31.1
Right pulmonary artery	16.27	37.5

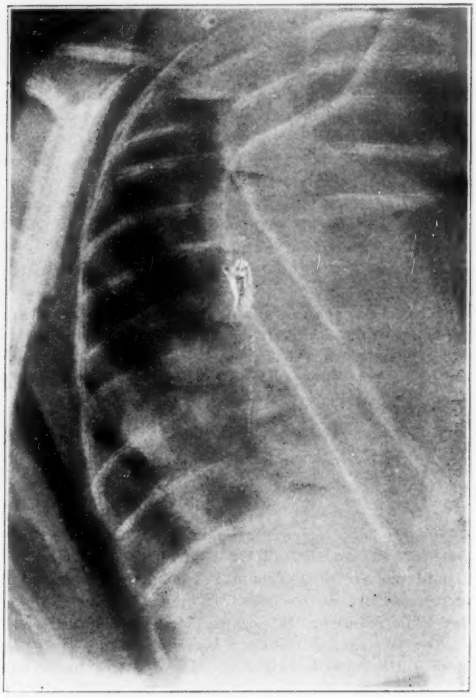

Fig. 4.—Tip of catheter in a right-sided aorta, having passed through a ventricular septal defect.

Because the experience of Dexter and his co-workers in the previously mentioned cases, an exploration was thought advisable even though catheterization had showed only an interventricular septal defect. At operation, the cause of the to-and-fro murmur was found to be a pulmonary arteriovenous fistula at the interlobar fissure on the left side. Also present was a common truncus arteriosus; the left pulmonary artery arose from it, and the right pulmonary artery arose from the left pulmonary artery.

Associated with Patent Ductus Arteriosus: J. P., a housewife of 21 who had had a heart murmur since infancy, came to the hospital for evaluation of the murmur.

She had never had dyspnea, cyanosis or other symptoms referable to the heart. The systolic arterial pressure was 125, and the diastolic pressure was 80. The heart was enlarged to the left midaxillary line, and a thrill was felt over the precordium. A grade 4 to-and-fro machinery murmur was present in the pulmonic area. Roentgenograms revealed severe cardiac enlargement and a pulmonary "hilar dance." A left ventricle hypertrophy pattern was noted on the electrocardiographic tracing. The catheter was passed into the superior vena cava, the right atrium, the right ventricle and the pulmonary artery. The catheter was then withdrawn into the right ventricle and passed through a ventricular septal defect into the aorta and the left carotid and subclavian arteries. An estimate of the oxygen content in the various sites showed 12.31 volumes per cent in the right atrium, 18.04 volumes per cent in the right ventricle and 18.17 volumes per cent in the pulmonary artery.

Patent ductus arteriosus was diagnosed because of the typical murmur and interventricular septal defect because of the differential in oxygen content and the passing of the catheter through the defect. At operation, a patent ductus arteriosus was found and ligated. After operation, a grade 2 systolic murmur persisted in the third and fourth left interspaces in the parasternal line. The to-and-fro murmur was gone.

Over a five month postoperative observation period, there was a pronounced decrease in cardiac size and an abolition of the pulmonary hilar dance.

Associated with Right-Arched Aorta: Y. B., a girl of 2, was studied because of tachycardia, underweight and a heart murmur. She had been cyanotic once for twelve hours when, at the age of 1 year, she had chickenpox with otitis media. There was no clubbing. The heart was slightly enlarged to the left. A loud, harsh systolic murmur was heard in the third left interspace parasternally. The catheter could not be passed into the pulmonary artery but was passed from the right ventricle into the left ventricle and into a right arched aorta (fig. 4).

Catheterization studies of the heart revealed the following data:

Site	Oxygen, Volumes %	Blood Pressure
Right atrium	14.65	25-30/15-20
Right ventricle	13.71	75-80/40-50
Aorta	17.80	100-112/70-80

The diagnosis was interventricular septal defect and right arched aorta.

Patent Ductus Arteriosus: P. L., a white boy of 4, had developed slowly, not walking until the age of 22 months. His mother remarked that he would always "take it slow, like an old man." Physical examination showed a small, underdeveloped child weighing 35 pounds (15.9 Kg.). There was no clubbing or cyanosis. The left side of the chest was prominent. Over the base of the heart, a systolic thrill could be palpated. There was a harsh, grade 4 systolic murmur in the second and third left interspaces, transmitted to the left side. At the fourth left interspace, there was a questionable diastolic component. However, the phonocardiogram clearly indicated the diastolic murmur (fig. 5). The second pulmonic sound was accentuated. The electrocardiogram was normal. Fluoroscopic examination showed an enlarged cardiac shadow and a "hilar dance." Previously, the diagnosis had always been that of an interatrial septal defect because of the absence of a typical machinery murmur. However, catheterization studies revealed the oxygen content of the blood to be 10.8 volumes per cent in the superior vena cava, 10.4 volumes per cent in the right atrium, 10.3 volumes per cent in the right ventricle, 12.6 volumes per cent in the right pulmonary artery and 13.6 volumes per cent at the bifurcation of the pulmonary artery. The patient subsequently had a large patent ductus ligated.

The condition of the patient had been misdiagnosed because the diastolic component of the murmur was not easily elicited. The case illustrates the value of stethocardiography and cardiac catheterization. The child was seen for a follow-up period of several months. All murmurs had disappeared, and, for the first time, he was gaining weight. His activity had increased greatly.

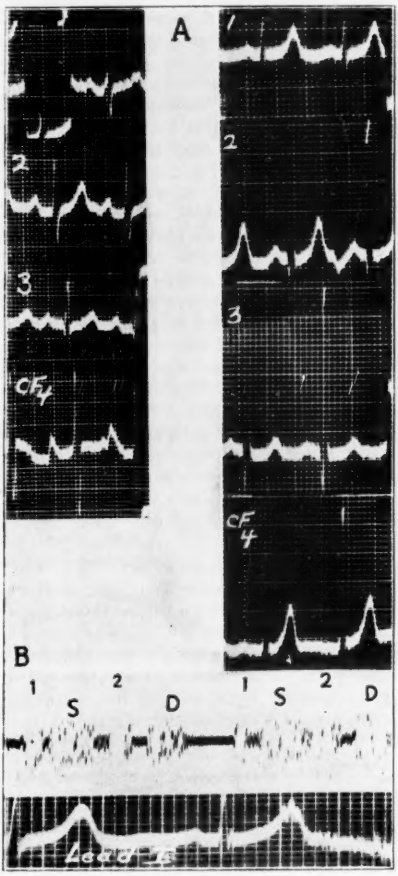

Fig. 5.—*A*, electrocardiographic tracing recorded in standard leads I, II, III and CF_4 in cases of patent ductus arteriosus. *B*, phonocardiogram recorded in the pulmonary region revealing the presence of a systolic and a diastolic murmur, although auscultation revealed only a systolic murmur. Photographs from Brooke General Hospital, United States Army.

J. M., a white boy of 22 months, had been delivered normally, weighing 7½ pounds (3.5 Kg.). A "heart murmur" was discovered at the age of 2 months. The child had had frequent infections of the upper respiratory tract, lasting two

to three weeks and accompanied with temperatures as high as 103 to 105 F. for one or two days. There had been no cyanosis. Physical examination showed a small white boy, weighing 22½ pounds (10.2 Kg.). The left side of the chest was more prominent than the right, and there were pronounced visible pulsations over the left side of the precordium. The heart was enlarged to percussion both to the right and to the left. A palpable, pronounced systolic thrill was present over the left side of the precordium. A harsh, grade 5 systolic murmur and a high-pitched grade 3 diastolic murmur were best heard over the second and third left interspaces and were transmitted to the apex. A questionable presystolic murmur was present at the apex. Fluoroscopic examination showed enlargement of the left and right ventricles. The pulmonary area pulsated actively. The stream of barium sulfate was deviated in the region of the left atrium. The electrocardiogram showed a first degree heart block, a rate of 90 beats per minute and a P-R interval of 0.22 second. The QRS interval in leads I and II was diphasic. The diagnosis of patent ductus arteriosus and possible rheumatic heart disease was made at that time. The child was followed closely; the condition did not improve. It was believed that the cardiomegaly was increasing. Because of the uncertain diagnosis it was decided to catheterize the boy.

The oxygen content values were as follows: superior vena cava, 8.7 volumes per cent; right atrium, 8.6 volumes per cent; right ventricle, 8.6 volumes per cent; right pulmonary artery, 14.4 volumes per cent, and left pulmonary artery, 18.8 volumes per cent. The patient was operated on, and a large ductus was ligated. When the patient was seen three months later, the change was remarkable. The chest wall was quiet, the thrill was not felt and all murmurs had disappeared. On fluoroscopic examination, the pulsations of the heart were found to be normal. An electrocardiogram still showed first degree heart block. At the time of this report, the patient has gained weight, has been rather active and has had no respiratory infections since his discharge from the hospital. Because of the first degree block rheumatic heart disease could not be excluded from the diagnosis, but the patient apparently had been having most of his difficulty because of a large patent ductus.

J. L., a male physician of 24, was known to have had a heart murmur at least since the age of 6 or 7. He had developed normally and had had no cardiac disorders. Results of the examination were normal except for a grade 2 systolic murmur at the second, third and fourth left interspaces in the parasternal line and at the apex. Fluoroscopic examination of the chest revealed normal conditions, as did the electrocardiograms. A stethogram revealed only a systolic murmur.

Catheterization studies of the heart revealed the following data:

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	14.28	.....
Right atrium	14.34	8/4
Right ventricle (apex)	14.63	24-30/10-12
Right ventricle (base)	14.58	.....
Left pulmonary artery	20.30	.....
(2 samples)	19.84	19/10

A diagnosis of patent ductus arteriosus was made; the operation has not been performed at the time of writing.

The diagnosis of a patent ductus arteriosus is made when a significant increase over that of the right ventricle is noted in the oxygen content of the pulmonary artery. Samples of blood must be taken fairly close to the hilar region in the pulmonary area to avoid getting capillary blood which has already been oxygenated.

In the majority of our cases of patent ductus arteriosus, the pressures in the right ventricle and in the pulmonary artery were within normal limits or only slightly increased. In 4 of the series of cases of patent ductus arteriosus, only systolic murmurs were audible; in 2, there was stethographic evidence of a diastolic component, and in 2 there was not. In 3 of the cases operation was performed, the presence of the ductus was confirmed and the murmur disappeared. An operation has not been performed in the fourth case at the time of writing. In about half the cases there was a significant drop in the systemic diastolic pressure after exercise. In 3, systolic murmurs were found to persist after ligation Repeated catheterization studies are planned in these cases.

Cyanotic Conditions.—Tetralogy of Fallot: Uncomplicated: D. A., a girl of 4½ years had been born a blue baby and at 3 months had had a severe attack of congestion of the lung with severe cyanosis. The patient had persistent mild cyanosis which had been exaggerated by two more episodes of pulmonary congestion. She frequently squatted to get her breath after walking a short distance. She had considerable limitation of her physical activities.

Physical examination showed an undernourished, underdeveloped, cyanotic white girl. Moderate suffusion of the conjunctivas was present. No definite cardiac hypertrophy was noted on examination. A harsh, grade 4 systolic murmur was heard over the precordium with its maximum intensity in the second and third left interspaces in the parasternal line. No definite diastolic component was heard. Some clubbing and cyanosis of the nails was noted. Roentgenograms revealed questionable evidence of hypertrophy of the right ventricle. No pulmonary window was demonstrated. Electrocardiograms revealed right axis deviation. The hemoglobin content, as determined by the photoelectric cell method, was 18.5 Gm. per hundred cubic centimeters of blood, and the erythrocyte count was 5,700,000 per cubic millimeters.

Venous catheterization of the heart revealed the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %	Blood Pressure
Superior vena cava	11.03	30.5	.....
Right atrium	11.51	31.7	1-2/0
Right ventricle	12.71	31.3	78/4
Right pulmonary artery	13.23	34.0	3/2
Femoral artery	24.20	17.2	.....

An increase in oxygen content in the right ventricle over that in the right atrium was somewhat suggestive of a left to right shunt, and definite evidence of a septal defect was obtained by passing a catheter into the pulmonary vein, with its greatly increased oxygen content. The combination of a large increase in pressure in the right ventricle and an extremely low pressure in the pulmonary artery was evidence of stenosis of the pulmonary infundibulum. The lowered oxygen saturation (72 per cent) in the femoral artery, in conjunction with the electrocardiographic and roentgenographic evidence, completed the diagnosis of tetralogy of Fallot.

A Blalock operation with anastomosis of the left subclavian artery and the left pulmonary artery was performed, with good results.

Associated with Patent Ductus Arteriosus: A case of cyanosis was recorded in which the catheterization findings were similar except that there was an increase of the oxygen content from the right ventricle (14.1 volumes per cent)

to the right pulmonary artery (18.7 volumes per cent). We believe that this difference indicates an associated patent ductus arteriosus. The oxygen saturation in the femoral artery was 81 per cent; no operation has been performed at the time of writing.

It is not to be expected that the tetralogy of Fallot can be recognized in its entirety by study with the venous catheter alone. Dextroposition of the aorta is largely a morphologic diagnosis; the condition is functionally indistinguishable from a ventricular septal defect in studies with the venous catheter. Hypertrophy of the right ventricle is perhaps best indicated by the electrocardiograms. The catheter may pass from the right ventricle through the stenotic pulmonary valve into the pulmonary artery or through the septal defect into the aorta. In the former instance, pulmonary stenosis may be recognized by the presence of a higher systolic pressure in the right ventricle than in the pulmonary artery. In the latter instance, pulmonary stenosis may be assumed to be present if the systolic pressures in the aorta and the right ventricle are identical (Dexter [12]). Thus, intracardiac catheterization may be used in studying patients with congenital cyanotic heart disease to ascertain the presence or absence of associated left to right shunts (especially patent ductus arteriosus) which may be increasing pulmonary blood flow. Too, the procedure may make available information about the pulmonary valve and artery and about the amount of flow through these structures.

Recent studies by Blalock and Taussig [1b] which led to the surgical treatment of congenital heart disease and cyanosis indicated the physiologic importance of a diminished rate of pulmonary blood flow in the production of anoxemia. As observed by Bing and others,[13] it is important to study quantitatively the changes in pulmonary blood flow in such conditions in order to correlate the primary abnormal factor with the accompanying hemodynamic and respiratory alterations. The practical significance of preoperative recognition of pulmonary stenosis and atresia makes it advisable to study the results of physiologic tests.

The essential factor in any operation on a patient with congenital cyanotic heart disease is to direct systemic arterial blood into the pulmonary artery so that an adequate proportion of the blood stream is oxygenated. The operation should be undertaken only when pulmonic circulation is inadequate and when systemic and pulmonary arteries can be used for, or adapted to, the anastomosis. By the method of venous catheterization and by exercise and respiratory tests, Bing and his associates [14] studied many cases of tetralogy of Fallot and found that

13. Bing, R. J.; Vandorn, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease: I. Procedures, Bull. Johns Hopkins Hosp. **80**:107, 1947.

14. Bing, R. J.; Vandorn, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease: II. Results of Pre-Operative Studies in Patients with Tetralogy of Fallot, Bull. Johns Hopkins Hosp. **80**:121, 1947.

a collateral circulation frequently develops which is not revealed by application of the direct principle (Fick[15]), using the venous catheter. By utilizing certain formulas, Bing and his co-workers were able to evaluate, to a certain degree of accuracy, pulmonary artery flow, systemic blood flow, pulmonary capillary flow and collateral circulation to the lungs, among other processes. In 48 cases of tetralogy of Fallot, the results of these tests demonstrated a reduction in pulmonary artery of 1,000 to 2,000 cc. below the normal cardiac index, depending on the degree of stenosis. In most of the cases, the systemic flow exceeded that through the pulmonary artery, indicating that the over-all direction of the intracardiac shunt was from right to left. The value of a combined determination of pulmonary artery flow and pulmonary capillary flow was demonstrated in 4 cases in the series in which clinical evidence suggested a patent ductus in addition to pulmonary stenosis. In cases of this type, the volume of flow through the ductus is represented by the difference between the pulmonary capillary flow and that in the pulmonary artery. An estimate of the rate of blood through the patent ductus is of considerable importance, as surgical construction of an additional ductus by the Blalock-Taussig operation may be indicated if the natural anastomosis is too small.

Common Atrium with Possible Tricuspid Atresia: B. T., a woman of 18, had been born a blue baby and had continued to be moderately cyanotic. Progressive clubbing of the fingers and toes had been noted by the patient. She was able to walk three to four blocks without undue shortness of breath and occasionally danced. For the past few months, there had been slight intermittent swelling of the ankles.

Physical examination showed a cyanotic, slender, somewhat underweight white woman with pronounced clubbing of the nails. The left border of the heart was at the anterior axillary line. There were no murmurs present. There was a sinus rhythm, the rate being 102 beats per minute. The blood pressure was 98 systolic and 74 diastolic. The rest of the physical examination was essentially noncontributory.

Electrocardiograms, including all precordial leads, revealed hypertrophy of the left ventricle. Stethograms failed to show any murmurs. Roentgenograms of the chest revealed suggestive evidence of hypertrophy of the left ventricle. The pulmonary artery could not be identified.

Venous catheterization studies yielded the following data:

Site	Oxygen, Volumes %	Carbon Dioxide, Volumes %	Blood Pressure
Superior vena cava	10.79	40.0	.....
Right atrium or common atrium	12.72	35.0	15/10
Right atrium or common atrium	10.31	49.0	.....
Site of vigorous pulsation, apparently just inside right ventricle	12.50	35.0	?
Pulmonary vein	20.97	23.8	8-10/3-4
Femoral artery	24.46 (saturation, 98%)		

15. Fick, A.: Ueber die Messung des Blutquantums in den Herzventrikeln, Verhandl. d. phys. med. Gesellsch. zu Würzb. **2**:16, 1870.

The catheter could be seen coiled in the large atrial chamber. Various oxygen values were observed; an increase of 1.92 volumes per cent of oxygen in the atrium over that in the superior vena cava was noted, suggesting an atrial defect with a left to right shunt. The catheter was passed into a pulmonary vein entering the right border of the heart. Multiple attempts were made to insert the catheter into the right ventricle; on one occasion, a most vigorous pulsation was noted in the tip of the catheter as it was thought barely to have entered the right ventricle, but pressure values could not be obtained. However, samples indicated that the values for oxygen content were similar to the higher values in the atrium. The tip of the catheter buckled each time an attempt was made to push the catheter farther into the ventricle.

We considered the possibility of a large defect in the atrial septum accounting for an intermingling of the blood and the possible production of cyanosis. Oxygen saturation in the femoral artery was reduced to 68 per cent. A pulmonary vein was found to be emptying into what appeared to be the common atrium. Because of the difficulty in passing the catheter into the right ventricle and because of the electrocardiographic and roentgenographic evidence of hypertrophy of the left ventricle, a diagnosis of possible tricuspid stenosis or atresia was also entertained in addition to that of the atrial septal defect. A similar case was recently reported by Geraci and his associates.[16]

Special Conditions.—Dilated Pulmonary Artery with Hypoplastic Aorta: R. R., a white man of 43, was admitted to the hospital complaining of having had shortness of breath for about three months. The present illness had begun approximately one and one-half years before, when he had been admitted to another hospital because of an abnormal roentgenogram of the chest; the condition was diagnosed as "heart disease," according to the patient. In June 1947, a chest cold developed. The patient was hospitalized, but the condition cleared and he was discharged. After this, he first noticed dyspnea on exertion, substernal pain that occasionally radiated to both shoulders and arms and several episodes of nocturnal dyspnea.

Physical examination showed a small, fairly well developed white man in no distress. The blood pressure was 135 systolic and 80 diastolic. The chest showed some slight prominence of the left side of the precordium. The heart was not enlarged to the left on percussion, and no thrills were felt. A short, grade 1 systolic murmur was heard over the second left interspace but was not always constant and showed no transmission.

The electrocardiogram was slightly abnormal, showing a deep S_I, a diphasic T_{II} and an inverted T_{III} wave. The P_{II} wave was pointed and prominent. Fluoroscopy showed a greatly dilated and pulsating pulmonary conus with dilated left and right pulmonary branches. The aortic knob was somewhat hypoplastic (fig. 6). Catheterization studies showed the oxygen content to be equal in all the chambers. The patient required no specific treatment other than rest.

Because of the clinical and roentgenographic findings and the results of catheterization a diagnosis of *"grosse pulmonaire—petite aorte,"* as made by

16. Geraci, J. E.; Dry, T. J., and Burchell, H. B.: Atrial Septal Defect and Probable Tricuspid Atresia in Adults, Proc. Staff Meet., Mayo Clin. **23**:510, 1948.

Laubry and his associates[17] in 1941, was entertained. They presented data concerning 39 patients personally seen by them who had shown the same syndrome as that of interatrial septal defect. Their failure to find a defect in 7 of the 8 cases at necropsy led them to conclude that malposition of the septum in the fetal truncus arteriosus was the etiologic factor. The final diagnosis in each case was dilated pulmonary artery and hypoplastic aorta.

Pulmonary Arteriovenous Aneurysm: A. M., a woman of 20, gave a history of having had a mild degree of cyanosis since birth. Starting one year before the patient's admission to the hospital, sporadic, transient, unconscious "spells" had begun to develop; at times, they were convulsive in type. Their frequency increased considerably during the year before admission, and two of the spells were accompanied with hemoptysis. The patient's gums bled rather easily for a few weeks before admission. There was mild limitation of her physical activity.

Physical examination revealed a listless, moderately cyanotic woman with pronounced clubbing of the finger nails and toe nails. A small hemorrhagic lesion was noted on the lower lip. Several prominent veins were noted in the mucous

Fig. 6.—Teleroentgenograms revealing a dilated pulmonary artery and a hypoplastic aorta (*"grosse pulmonaire, petite aorte"*).

membrane lining the mouth. Marked venous engorgement was noted on funduscopic examination. The heart was not enlarged, the rhythm was regular and no murmurs were heard. The rate was 86 beats per minute. There was a rapid, 40 point drop in the systolic and diastolic arterial pressures on standing; the previously normal blood pressure had been 118 systolic and 72 diastolic. Gross examination of the lung failed to reveal any abnormalities, and no murmurs were heard.

A teleroentgenogram revealed a normal-sized heart with a lesion in the lower field of the right lung, in which there was a suggestion of a few cryptic cavities (fig. 7). Pulmonary markings were increased in both lung fields. Electrocardiograms revealed a vertical heart but were otherwise unremarkable. The hemoglobin value, as determined with the photoelectric cell, was 22.0 Gm. The erythrocyte count was 7,400,000.

17. Laubry, C.; Routier, D., and Heim De Balsac, R.; Grosse pulmonaire: Petite aorte; Affection congénitale, Bull. et Mém. Soc. méd. d. hôp. de Paris **56**:847, 1941.

Venous catheterization studies revealed the following data:

Site	Oxygen, Volumes %	Blood Pressure
Superior vena cava	13.2	...
Right atrium	13.6	5/3
Right ventricle	13.5	20/0
Right pulmonary artery	13.5	3/0
Left pulmonary artery	13.4	3/0

It was thought that this patient had a pulmonary arteriovenous fistula, despite the absence of a continuous murmur over the lung shadow or at any place in the

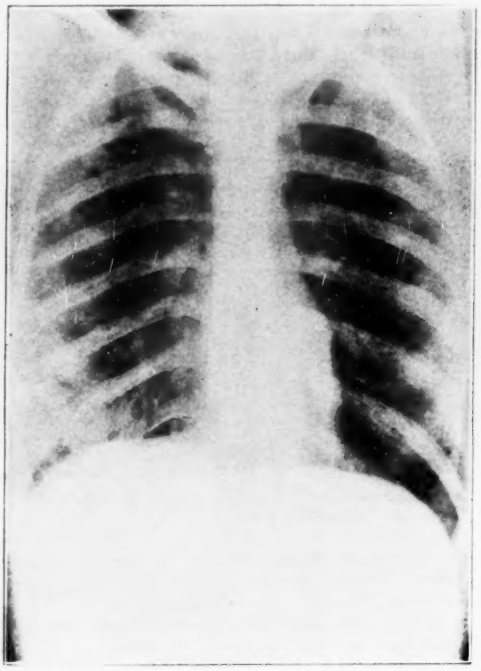

Fig. 7.—Teleroentgenogram revealing a normal-sized heart and an infiltrative area in the base of the right lung. The patient had a pulmonary arteriovenous aneurysm.

hilar regions. The history of convulsions, hemoptysis and cyanosis coupled with polycythemia and a shadow of the parenchyma of the lung suggested the clinical diagnosis. Catheterization studies were within normal limits. An attempt at the administration of iodopyracet injection (diodrast®) with the catheter in the right pulmonary artery had been planned, but the patient stated that she felt a convulsion coming on at the end of the catheterization, and further manipulation was abandoned. The convulsion, however, failed to materialize. (It is thought that catheterization studies would be of definite benefit in such cases to localize the site of an arteriovenous anastomosis.) Within the next few days, the patient

went into a profound coma and died before surgical intervention was attempted. Postmortem studies revealed a large pulmonary arteriovenous aneurysm.

Normal Hearts.—The next group of patients studied was composed of children with heart murmurs that were thought by some examiners to be indicative of congenital heart disease. However, normal values for pressures and gas volumes were obtained. Venous catheterization studies may be of definite value in ruling out a diagnosis of suspected congenital heart disease and may greatly allay the fear of parents.

Diagnosis Impossible Because of Insufficient Data.—In the remaining 3 cases, insufficient data were obtained to make a diagnosis. In 2 of these, in which patent ductus arteriosus was suspected, we were unsuccessful in getting the catheter into the pulmonary artery. In the third case, we were unable to get the catheter into the right ventricle.

Complications.—We have had no major complications. Occasionally ventricular premature beats appear, especially when the catheter is close to the atrioventricular valve, but they do not persist. Atrial fibrillation [18] has been reported, but this was controlled, and it disappeared when the catheter was removed. Superficial phlebitis of the antecubital veins developed in 3 cases but responded readily to local therapy. In 1 case, while using a smaller-sized catheter, we encountered plugging of the catheter and were forced to discontinue the procedure. On a few occasions, we have found it necessary to change catheters. In 2 cases, in children, the smallness of the veins prevented introduction of the catheter. In 1 case, there was retention of the catheter and it had to be removed with the patient under anesthesia; in another case, we were unable to get the catheter past the first rib, perhaps because of an associated abnormality of the venous system.

SUMMARY AND CONCLUSION

Intravenous catheterization of the heart in 72 cases of suspected congenital heart disease is discussed. The method and the application of it to the more accurate diagnosis and the study of the disturbed physiology of congenital heart disease are presented with a notation of the complications that may be encountered. The results of this method in 69 cases are given, and several detailed case reports representative of the acyanotic, potentially cyanotic and cyanotic types of heart disease as well as of pulmonary arteriovenous aneurysm and dilated pulmonary artery with hypoplastic aorta are given.

Venous catheterization has opened new possibilities for the recognition of many congenital defects, for elucidating the hemodynamic changes and for assisting in rendering a prognosis by defining the nature and the physiologic magnitude of the defects. Precise diagnosis is of such importance that all patients whose condition is doubtful should be studied with available diagnostic technics.

This work was aided by Dr. L. Vaughn, roentgenologist, and Miss Anne Bray and Miss Peggy Gallagher, technicians.

18. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Seibe, R. E., and Evans, J. M.: Studies of Congenital Heart Disease: I. Technique of Venous Catheterization as a Diagnostic Procedure, J. Clin. Investigation **26**:547, 1947.

Book Reviews

Coronary Artery Disease. By Ernst P. Boas, M.D., and Norman F. Boas, M.D. Price, $6. Pp. 399, with 88 illustrations. Chicago: Year Book Publishers, 1949.

The Drs. Boas have written a commendable monograph on "Coronary Artery Disease." The arrangement is practical and logical, and the diction is clear. The authors' claim that the book is designed as a useful tool for the physician and that it is also sufficiently detailed to make it of interest to the cardiologist is valid. The extensive bibliography is well selected, and, in the reviewer's opinion, the appearance of supporting references as footnotes on the appropriate pages has distinct advantages.

The anatomic, embryologic, physiologic and pathologic aspects of the coronary circulation are covered in the earlier chapters. The approach to the subject is that of the clinician who has had wide first hand experience with diseases affecting the coronary circulation and, through it, the myocardium. Emphasis is placed on the restorative and compensatory mechanism inherent in the coronary circulation.

The opinions expressed on the diagnostic aspects of coronary heart disease are concise; yet, at the same time, they cover the variables in the pathologic aspects of coronary heart disease and the corresponding variables in the clinical picture. This is true of the acute episodes of the disease as well as of the more chronic phases of coronary insufficiency. The differentiation of the pain of angina pectoris from that due to noncardiac conditions producing pain in the thoracic structures is unusually well handled. The importance of recognizing what the authors refer to as "benign precordial pain," so frequently encountered in anxiety states either in association with, or often independent of, organic heart disease is well illustrated by a quotation (page 167): "The patient with true anginal pain reports very simply and without dramatic embroidery that walking, strain or excitement induces some form of sensation in the chest, or at times in the arm alone, which compels an arrest of activities. After a few minutes' quiet the distress is gone and the patient feels as well as ever. In contrast to this simple, clear story, the account by the individual with benign precordial pain is a highly colored version of sharp chest pains with all kinds of associated symptoms and vasomotor disturbances. He is not compelled to immobility, but lies down and rests and is overcome with bodily weakness, largely from apprehension."

The role of the electrocardiogram in the recognition, management and prognosis of coronary heart disease is supported by well selected illustrations. In the majority of instances, the authors use the precordial leads CR_2, CR_4 and CR_5 in conjunction with the standard limb leads. In discussing the outlook in coronary heart disease, the authors give a true perspective of the life history of coronary heart disease and point out the invalidity of most of the statistical data reflecting prognostic trends, as reported in much of the medical literature.

The authors are outspoken in their views on the actions of many drugs which have been and still are in use in the treatment of coronary heart disease. This material should be of assistance to interns and less experienced men of the profession who may be confused by the controversial statements and divergent claims made by many authors throughout the extensive literature on these subjects.

Sections dealing with treatment cover every phase of the disease. Here, again, the statements are clear and to the point. In any treatise covering a subject such as coronary heart disease it would be impossible to present opinions that would be unanimously accepted by all authorities. There is certainly no fault to

be found with the major issues presented, although there may be some difference of opinion about some of the minor ones.

In the reviewer's opinion, this book is one of the best contributions to the field of cardiology in recent years.

Symposium on Diseases of the Skin. The Medical Clinics of North America. Chicago number, January 1949. Pp. 292, with 134 illustrations. Philadelphia: W. B. Saunders Company, 1949.

This volume comprises a symposium on diseases of the skin, the contributors, with the exception of Drs. O'Leary, Curtis, Grekin and Duncan, being dermatologists residing in Chicago.

Subject matter was evidently chosen because of special interest in certain fields on the part of the various well known contributors. In general, each author discusses his problem from the standpoint of clinical manifestations, laboratory findings, etiology, differential diagnosis and treatment. Actual case reports and illustrations are included in many of the papers.

Dr. Becker presents a clear and logical interpretation of neurodermatitis and pruritus. Dr. O'Leary's discussion of dermatomyositis is especially interesting from the standpoint of differential diagnosis. Drs. Curtis and Grekin review the problem of sarcoidosis and include an informative paragraph on involvement of the eye. Drs. Rothman and Walker discuss the salient features of both diffuse and localized scleroderma. Dr. Senear gives a short but lucid interpretation of dermatitis exfoliativa, unburdened with descriptions from the older literature. Dr. Ebert's discussion of the herpes problem and Dr. Rattner's discussion of pemphigus are well done. Dr. Rostenberg's presentation on cutaneous allergic disorders reflects his intense interest in and personal interpretation of allergy.

Other problems discussed are skin cancer, under several titles, by Drs. Oliver, Squire, Finnerud and Duncan; nail changes following the use of "base coats," by Dr. Mitchell; disseminated lupus erythematosus, by Drs. Graffin, Taylor and Hass; atopic dermatitis, by Dr. Hetreed; common nevi, by Dr. Webster; cutaneous pharmacodynamics of vehicles and drugs, by Dr. Rothman and Dr. Shapiro, and dermatopathology as a window to internal disease, by Dr. Caro.

The volume is comparatively small, in large type and consisting of 292 pages, including 134 well chosen illustrations. It does not attempt to review all diseases of the skin, but the articles are interesting, currently authoritative and easy to read. This symposium should find interested readers in the fields of general practice and internal medicine as well as dermatology.

Clinical Auscultation of the Heart. By S. A. Levine, M.D., and W. P. Harvey, M.D. Price, $6.50. Pp. 327, with 286 illustrations. Philadelphia: W. B. Saunders Company, 1949.

A hundred and three years ago, Dr. Henry I. Bowditch of the Harvard Medical School wrote "The Young Stethoscopist," in which he described all that he could of auscultation of the heart; indeed, his colleague, Dr. Henry J. Bigelow, reviewing the book in *The Boston Medical and Surgical Journal,* complimented Dr. Bowditch highly by saying that he had booked Laennec up to date and had compressed his genius into a prodigiously small volume.

Now, two other authors from the Harvard Medical School continue "to book Laennec up to date." They have written an ingenious sequel to "The Young Stethoscopist," in which they discuss auscultation of the heart, not by means of the ear alone but by combining what the ear can hear with what the electrocardiograph reveals in regard to cardiac action and with what the eye sees of the heart sounds as they are photographed electrically.

The result is a book of practical value and of great interest. The authors answer many of the riddles which Dr. Bowditch found so perplexing: among others, the causes of change in character of the heart sounds, the cause of a third or fourth heart sound, the significance of various cardiac irregularities and the clinical importance of the *"bruit de souffle,"* the *"bruit de rape"* and the *"bruit de scie"*—terms invented by Laennec in the days when the well brought up post-graduate student went to Paris to learn the art of physical examination.

Interspaced among many excellent illustrations is a great deal of clinical wisdom. Dr. Bowditch advises his readers: "Do not trouble yourself so much about nice distinctions of sound; but observe accurately, first, where the sounds are heard; second, where the focus of them is; and third, their combination with other physical and rational signs." Drs. Levine and Harvey elaborate on the text in a happy vein.

Without further description of the new book, it is cheerfully advocated, in the words of the first Boston reviewer of "The Young Stethoscopist," as a book to be recommended with the conviction that whoever studies its precepts will be a wiser practitioner than he was before.

Medical Etymology. By O. H. Perry Pepper, M.D. Price, $5.50. Pp. 263. Philadelphia: W. B. Saunders Company, 1949.

Dr. Pepper has done a great service to physicians and to medical students in compiling this extremely useful book on the etymology of medical terms. As the author says in the preface, it is not intended to be a dictionary; no roots are analyzed, declensions are not discussed, there are no elaborate discussions of gender. On the contrary, Dr. Pepper sticks strictly to business and for the most part simply gives the meaning of the Latin or Greek word from which a medical term is derived. This is done with true Johnsonian terseness, barring an occasional comment or brief discussion which, indeed, is also worthy of the Great Lexicographer. Of course, the sad part of all this is that the very need of such a vademecum shows the depths to which modern education has fallen. A hundred years ago any second form boy (as Macaulay would have said) deserved and doubtless got a flogging for not knowing such elementary stuff. Dr. Pepper agrees with this opinion but accepts the theory that "classical education is a dead letter for those entering the medical sciences and 'nothing can be done about it.'" With this, the reviewer does not altogether agree. Wise men in all branches of education, including science, are realizing the need of reviving the means of firsthand acquaintance with the civilization from which our own is derived as well as realizing the value of the tremendous mental discipline which is to be gained from accurate translation of a foreign language. It has been said that the British won their battles on the playing fields of Eton; perhaps it was really in the classroom, struggling with Greek hexameter, that clear thinking and grit were acquired.

Be that as it may, "Medical Etymology" should certainly be on the required book list of every medical school at the present time.

Symposium on Cardiovascular Diseases, Especially Hypertension. Medical Clinics of North America (New York number), May 1949. Pp. 911, with 190 illustrations. Philadelphia: W. B. Saunders Company, 1949.

A symposium of cardiovascular diseases with emphasis on hypertension is featured in the New York number of the *Medical Clinics of North America*. The discussion opens with an encouraging article on the benign phase of hypertension, pointing out that it can exist for many years despite unfavorable roentgenographic

and electrocardiographic changes—a fact to be considered when evaluating either medical or surgical therapeutic results. There follows a group of articles on fundic alterations, electrocardiographic changes and capillary fragility as studied in hypertensive persons. Differential points between the electrocardiogram in hypertension and that in myocardial infarction are well demonstrated, as is the concept that metabolic and arteriosclerotic changes, and not hypertension per se, cause capillary fragility.

Therapy of the hypertensive patient is discussed in a series of articles covering both surgical and medical phases. The conservative regimen of sensible living habits, sedation and judicious administration of thiocyanate is offered as producing results comparable to the more radical procedures. On the other hand, the advocates of sympathectomy present statistics which warrant further consideration of this unsettled and controversial problem.

The remainder of the discussion of cardiovascular problems presents speculative and proved points in arteriosclerosis—the etiologic role of hormones and cholesterol, therapy and the relation of the disease to diabetes. In addition there are miscellaneous papers on psoriatic arthritis, on relapsing pancreatitis and on fluid and mineral balance in infantile diarrhea, all of which are adeptly written and serve to round out an excellent number of the *Medical Clinics of North America.*

Archives of Internal Medicine: The Epidemiology of Hemolytic Streptococcus. By Alvin F. Coburn and Donald C. Young. Price, $4. Pp. 229, with 31 illustrations and 51 tables. Baltimore: The Williams & Wilkins Company, 1949.

The authors of this book deserve high praise for the interesting way in which they have assembled a vast mass of material. As they state in the preface, the thought of making nationwide observations on streptococcal activity seemed of only academic interest until lately; the war, however, made the need of practical and essential significance.

Dr. Coburn and Dr. Young were in a position to follow a wise bit of Oslerian advice—"Observe, tabulate and record." In this monograph, therefore, they record the results of observing and tabulating the effect of the streptococcus on young men in training for Naval service.

They were helped in all possible ways: by epidemiologists, bacteriologists, clinicians and statisticians, as well as by patients themselves. The result is a valuable account of composite medical experience. It is interesting for a practicing doctor to read, for it describes so clearly how streptococcus infections are likely to spread through any community; it is an important work for physicians interested in public health, because so much valuable material is reported; it is a fine piece of medical literature for students because it is written clearly and concisely, and because it reveals how clinical research in the field of infectious disease can be conducted, what methods are available and how conclusions are drawn by the judicious and unprejudiced analysis of carefully accumulated data. On the whole, it is a contribution to medicine in which the Bureau of Medicine and Surgery of the United States Navy may well take pride.

Diagnosis of Viral and Rickettsial Infections. By Frank L. Horsfall Jr., M.D. Price, $3.75. Pp. 153, with 4 illustrations, 7 plates and 14 tables. New York: Columbia University Press, 1949.

On Jan. 29 and 30, 1948, a symposium on the diagnosis of viral and rickettsial infections was held in the New York Academy of Medicine. After brief introductory remarks by Dr. Horsfall, of the Hospital of the Rockefeller Institute, twelve papers were presented. These dealt with laboratory procedures usable in

studying viruses and with the diagnosis of mumps, the psittacosis-lymphogranuloma group of infections, primary atypical pneumonia, neuropathic virus infections, herpes simplex, rabies, dengue, infectious mononucleosis, Rocky Mountain spotted fever and infectious hepatitis. Each of the papers was presented briefly and pointedly by an authority on the topic under consideration. The volume in which the papers are compiled is informative and of unusual interest.

Those who enjoy attempting to trace the development of medical knowledge may recall that a similar symposium was held nearly a decade ago at the Harvard School of Public Health; although chief emphasis was laid on the significance of virus and rickettsial diseases in public health, laboratory procedures and diagnoses were included. Thus, the book, "Virus and Rickettsial Diseases," printed in 1940 and reporting the Harvard symposium, is interesting to study beside "Diagnosis of Viral and Rickettsial Diseases," printed nine years later. Either book alone deserves a place in any medical library; the two beside one another make a handsome pair. In comparing them, one feels that Hans Zinsser and other virologists who were active only a few years ago must be proud of the record.

George R. Minot Symposium of Hematology. Edited by William Dameshek, M.D., and F. H. L. Taylor, Ph.D. Price, $12. Pp. 984. New York: Grune & Stratton, 1949.

This is a notable volume, dedicated by a group of his friends to Dr. George R. Minot, who, besides being a Nobel prize winner, is a sociable person—the kind of man well liked by his pupils, associates and professional colleagues.

The book deals mainly with diseases of the blood; properly enough, it begins with a reprint of that historic paper written by Minot and Murphy in 1926, "Treatment of Pernicious Anemia by a Special Diet." Then follow articles on pernicious anemia, hemolytic anemia, other anemias, hemorrhagic diseases, leukemia, the cytology and biochemistry of the red and white cells and, finally, two papers on more general aspects of medicine, one from Gunnar Alsted of Copenhagen on peptic ulcer, and one from W. Richard Ohler of Boston on diabetic coma.

There are eighty-four articles in the entire collection; each is written by an authoritative worker in his field, and they are printed tastefully in a well designed and well illustrated volume. Every writer seems to have been stimulated to prepare his manuscript in a fashion sufficiently meticulous to satisfy Dr. Minot's respect for detail, accuracy and imagination. Thus, the result not only is a pleasing symbol of friendship for one of the leading internists and clinical investigators of his day but also is a valuable reference source for any one wishing to learn of the most recent advances in hematology.

Oral and Dental Diagnosis. By K. H. Thoma, D.M.D. Third edition. Pp. 563, with 776 illustrations. Philadelphia: W. B. Saunders Company, 1949.

The first edition of this book, 379 pages long and including 533 illustrations, appeared in 1936. A second edition, a little bigger and better than the first, was necessary in 1943. Now the third edition has appeared; the book has grown in stature to comprise 563 pages and 776 illustrations.

The basic model of the volume remains unchanged. It describes how important it is for physicians to examine the oral cavity properly, always bearing in mind that a variety of systemic disorders may make an early appearance in the mouth. It also describes, in great detail, oral diseases in general and their diagnosis and treatment in particular.

Both earlier editions were reviewed favorably in *The Journal of the American Medical Association* (**108**:1209 [April 3] 1937; **124**:469 [Feb. 12] 1944). THE ARCHIVES is glad to welcome the third edition and to emphasize what was stated in previous reviews, that the book is a textbook to be used by students and physicians as well as by dentists and oral surgeons. For if the field of dental medicine is to be opened widely, it must be explored adequately—not by specialists working in a narrow area but, broadly and extensively, by groups of physicians working together. From this point of view, the book is an important source of reference.

Manual of Medical Emergencies. By S. C. Cullen, M.D., and E. G. Gross, M.D. Price, $3.75. Pp. 267, with 29 illustrations. Chicago: Year Book Publishers, Inc., 1949.

The authors of this book are professors in the State University of Iowa College of Medicine and apparently enjoy teaching. They have assembled an admirable manual. As the title foretells, it deals with the treatment of the kind of emergencies which any doctor is likely to encounter—emergencies that require artificial respiration or the use of oxygen, circulatory emergencies, poisonings, burns, comas and serious anaphylactic reactions.

The book is written positively, it gives intelligent, readily understandable advice in regard to the management of a variety of accidents, and the fact that it is so dogmatic makes it all the more readable.

The illustrations are also helpful; a few cartoons that have been introduced are not particularly cogent.

The book is of a size and shape to fit easily into one's bag or pocket. On the whole it should be of great service, as its dedication suggests, to the general practitioner, who is expected to see all, know all and do all in the field of medicine.

Studies of Chronic Pyelonephritis. By Flemming Raaschou, M.D. Pp. 260, with 61 illustrations. Copenhagen: Einar Munksgaard, 1948.

This monograph was prepared as a doctor's thesis at the University of Copenhagen. It has been translated into English and gives a thorough and detailed account of chronic pyelonephritis.

The discussion of the history of the disease and its pathology is well written. The analyses of the age and sex distribution of pyelonephritis and of its frequency and its clinical course are adequate. Chief emphasis is placed on the author's studies on renal function, in which he describes his observations of glomerular and tubular function in a series of cases. He has used urea clearance and inulin and iodopyracet injection (diodrast®) in a variety of ways, attempting to prove what modern tests for renal function can demonstrate in the study of the pyelonephritic kidney. He gives a good summary of the literature.

On the whole, this is a painstakingly written volume. It should prove useful as a source of reference for those who, like the author, are interested in renal physiology and for those who wish to learn how transatlantic colleagues are attacking its complex problems.

Anales de la cátedra de clínica médica. (Volume II), 1947. By E. S. Mazzei, M.D. Annual publication of the University Clinic. Pp. 267. Buenos Aires: "El Ateneo," 1948.

The book is a collection of selected material for lectures to medical students. Little original material is presented, with the exception of a short and interesting article by de la Torre on the treatment of acute glomerular nephritis by the

intravenous injection of procaine hydrochloride (novocaine®). Three cases of acute glomerular nephritis following scarlet fever are described in which this treatment was given with spectacular results. The rest of the articles are mostly complete and excellent reviews of recent advances of American and French medicine. An article by Bergna on Hr factor is particularly exhaustive. American readers will find of special interest a well organized monograph by Reussi on bronchopulmonary topography and its applications to the studies of the pathology and treatment of pulmonary disorders. The format of the book is excellent; the bibliographic references are complete and well arranged.

An Atlas of Electrocardiography. By W. Dresseler, M.D., and H. Roesler, M.D. Price, $14. Pp. 503, with 439 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1949.

This atlas is not particularly different from others available. It consists of photographs of electrocardiograms presented on one page with clinical and other related data and the electrocardiographic data on the opposite page. This conventional procedure of making the tracing and the discussion available to the reader simultaneously is obviously a good one. Some interpretations are documented with postmortem findings. Unfortunately, the chest leads presented in most of the cases consist of CF and CR leads rather than unipolar leads. If these leads are to be presented the unipolar leads should not be excluded. As the authors state, the atlas is not intended for beginners; it may be of value to others.

Present Concepts of Rehabilitation in Tuberculosis. By Norvin C. Kiefer, M.D. Price, $3.50. Pp. 398. New York: National Tuberculosis Association, 1949.

This excellent book comprises a review and analysis of some 1,000 papers on the subject of rehabilitation in tuberculosis. Being really a series of abstracts it lends itself poorly to review; the main value is as a reference book. Here, in classified form, one finds material on such matters as agencies, types of program, and personnel. The book will be invaluable to public health officers and to all persons interested in tuberculosis.

Female Sex Endocrinology. By Charles H. Birnberg. Price, $4. Pp. 134, with 30 illustrations. Philadelphia: J. B. Lippincott Company, 1949.

This is a readable and concise handbook of female endocrinology. It is written so simply that lay women as well as medical students and practicing physicians of both sexes can learn from it. It gives an up-to-date account of its subject and explains some of the new terms and remedies that are achieving popularity. While not a great book, it promises to fill a useful purpose.

Food Poisoning. By G. M. Dack, M.D. Revised edition. Price, $3.75. Pp. 184 with 13 tables. Chicago: University of Chicago Press, 1949.

This is a brief monograph on food poisoning, written, with able assistance, by an authority on the subject. The data are presented in more or less the usual textbook of medicine fashion. It is to be recommended highly for clinicians, students and bacteriologists.

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1. Davis, F. W.: Amebiasis: Experience in the Johns Hopkins Hospital, 1936-1946, Am. J. M. Sc. 217:505 (May) 1949.
2. Manson-Bahr, P.: Some Tropical Diseases in General Practice: "A Post-War Legacy," Glasgow M. J. 27:123 (May) 1946.

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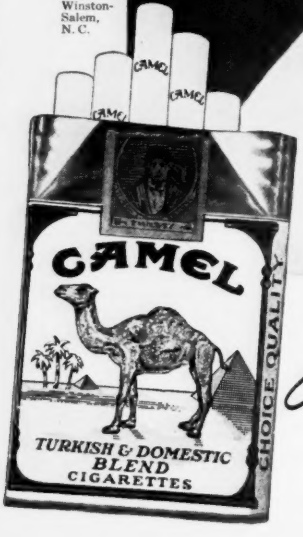

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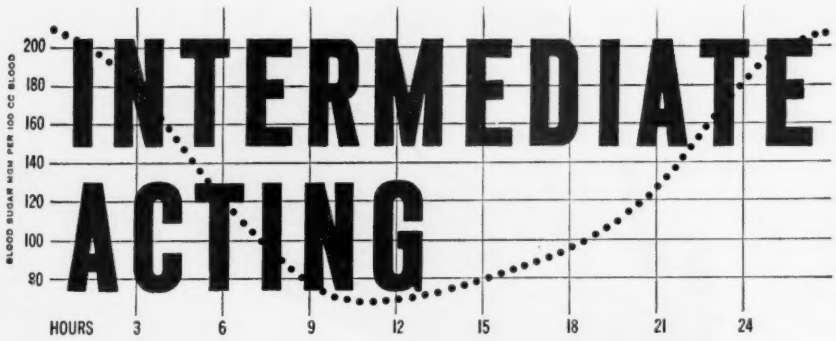

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948

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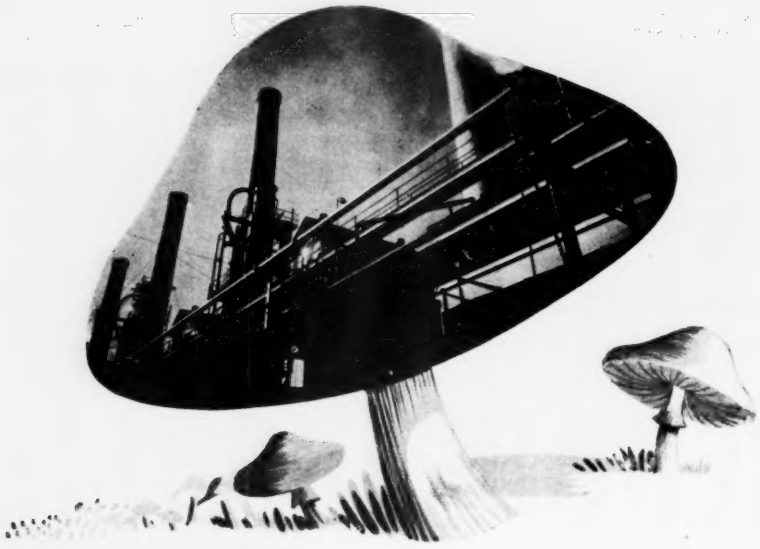

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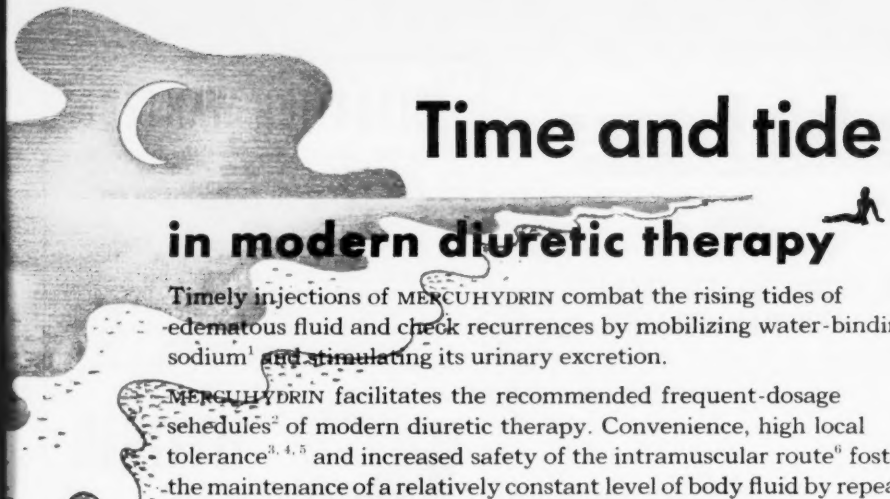

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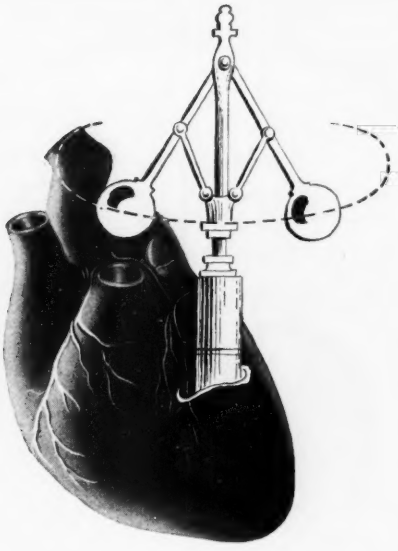

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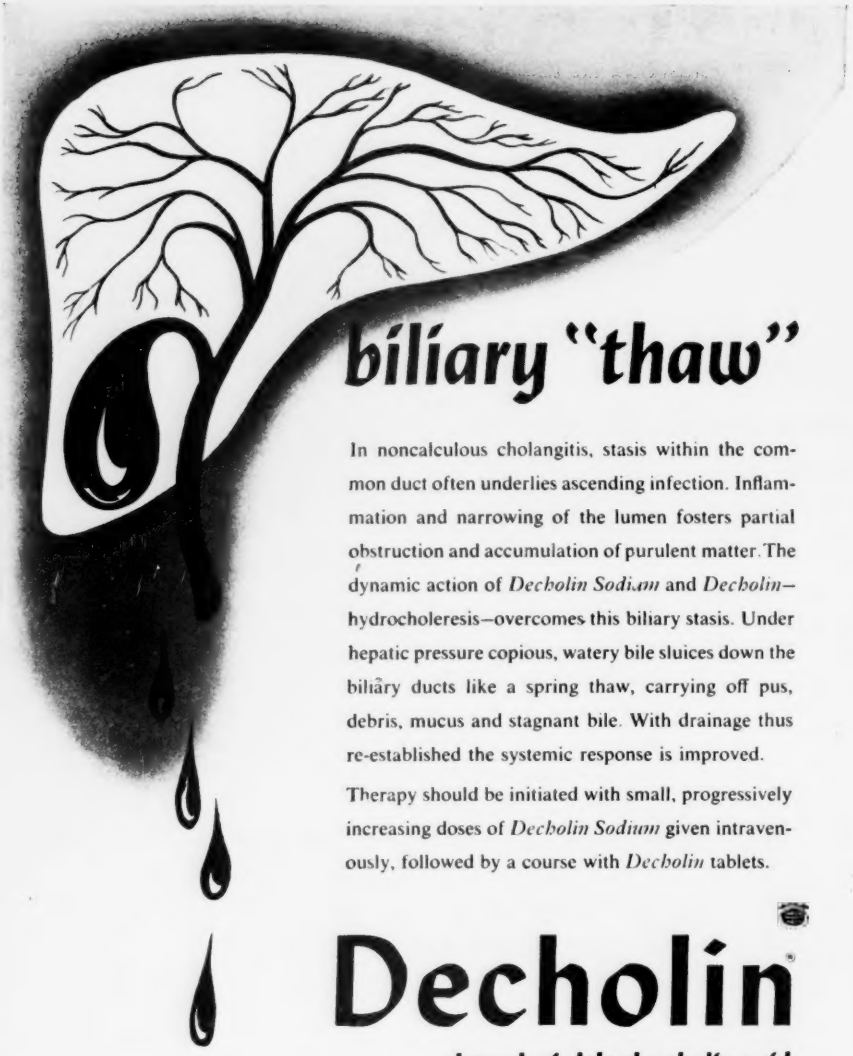

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